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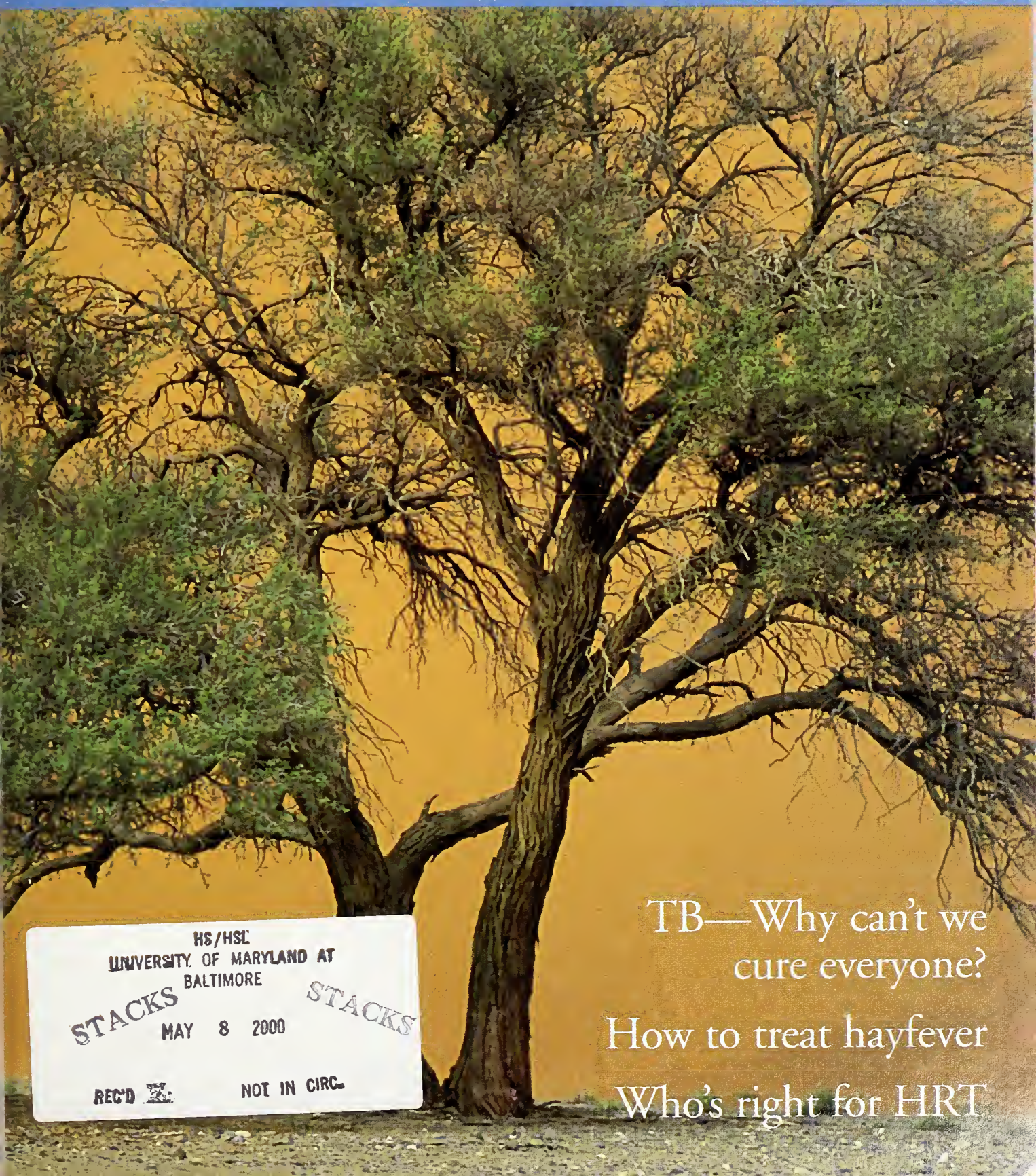

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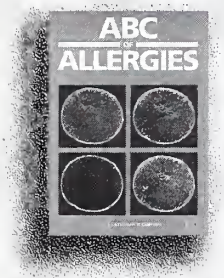

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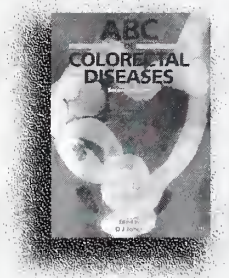

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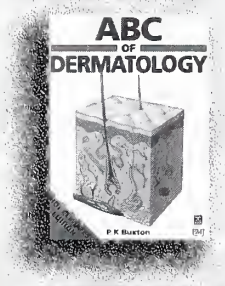

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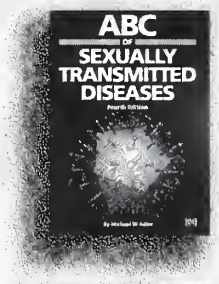

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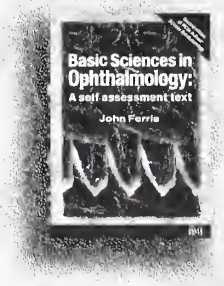

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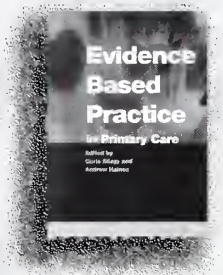

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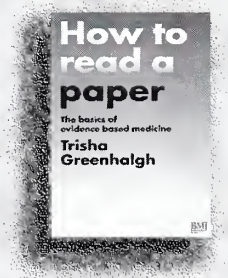

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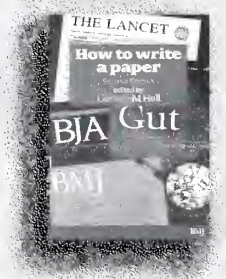

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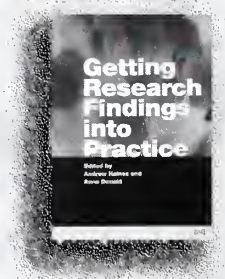

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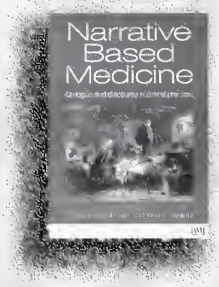

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This month in wjm

Children of Mexican mothers are at risk from poisoning

Unintentional poisoning is second only to falls as a cause of injury in children under 5 years old. Rates of poisoning are higher among Hispanic children. Previous studies suggest that cultural factors may play a role, with some children eating medicines manufactured in Mexico that do not have child-resistant packaging. On page 16, Dorothy Mull et al. describe an ethnographic study that involved questioning Mexican-born mothers now living around Los Angeles. The researchers visited homes and found that few households stored medicines safely and none had working childproof latches on cabinets. Iron, commonly taken accidentally by children, was often easily available and stored with food. In an accompanying commentary, Geri-Ann Galanti explains how ethnographic research is carried out and why, for some questions, it can tell us more than scientific trials.

VA hospitals penalized over lack of consent

Informed consent is the cornerstone of ethical research and should be obtained from patients in all studies. But in the nation's largest veterans' hospital, West Los Angeles VA Healthcare Center, federal regulators suspended research earlier this year amid claims that patients were undergoing moderate- to high-risk research procedures, such as cardiac catheterizations, without their consent. One patient was said to have refused on 2 occasions. Sara Thier on page 53 explains what went wrong, what's being done to correct it, and how other hospitals are also likely to have their research programs suspended.

How to fight tuberculosis worldwide

Directly observed therapy short course (DOTs) is the strategy adopted by the World Health Organization to cure people with tuberculosis. In part it involves watching people take their tablets, but for DOTs to work it needs an infrastructure to provide reliable diagnosis, drugs, recording of cases and outcomes, and government commitment to provide the resources to maintain the program. While DOTs is reported to have an 85% success rate, Anne Fanning argues on page 4 that it is not available to two-thirds of the world's population. While arguments often center on whether people should be detained for DOTs (see page 44 for a history of containment in Seattle), Fanning points out that nearly 7 million people with the disease do not have the choice to take the drugs voluntarily.

Allergic rhinitis can be treated effectively

Allergic rhinitis is a problem for 20 to 40 million Americans annually and can reduce productivity at work. The symptoms of itchy nasal passages, sneezing, and eye irritation can be deeply aggravating. But symptomatic treatment often comes at the cost of sedation, and the ideal therapy, environmental avoidance, is usually impossible. This month's Medicine Cabinet (page 31) details the pros and cons of various treatments, including side effects, and provides an essential guide to the pharmacotherapy of this common condition.

Breast is best but may be inconvenient at work

Most physicians believe that breastfeeding should be encouraged, but many women doctors find their own attempts to breast-feed at work hindered by unhelpful colleagues. On page 62, Anne Montgomery speaks out on her own frustrations at trying to breast-feed at work, and on page 55 Scott Gottlieb discusses 3 bills that aim to make women's rights to breast-feed their babies enforceable by law.

Loss of desire is the commonest sexual problem for women

The commonest sexual disorder among women is loss of desire, which can be caused by stress, fatigue, drugs, and depressive illnesses. On page 41, Josie Butcher explains that in the timetable of life, women may have loss of desire quite naturally due to childbirth and menopause. Physicians should remember that loss of desire can be triggered by such common drugs as tamoxifen, sedatives, and antidepressants. Loss of sexual desire can be resistant to treatment.

How narrative can teach us medical ethics

Stories can be powerful learning tools in medical ethics, says Anne Hudson Jones on page 50. Medical students could do well to read George Eliot's Middlemarch or F. Scott Fitzgerald's Tender Is the Night to develop virtue ethics and to understand what it means to lead a good life. Autobiographical accounts by patients are useful commentaries on autonomy and respect for persons. Doctors' narratives on physician-assisted suicides, such as the anonymous account of the hastening of a death through an overdose of analgesia, "It's over, Debbie," published in the Journal of the American Medical Association, have forced a reexamination of this controversial issue. A Cook County state's attorney took the journal editor to court to try to force him to reveal the doctor's identity.

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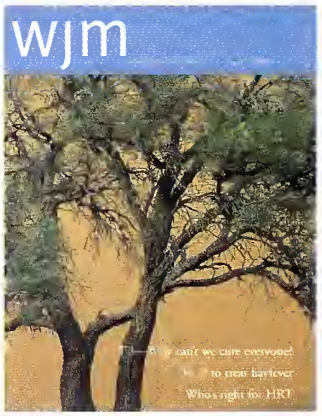

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Op-Ed

The DOTs strategy

More than just watching patients take their tablets

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Conflicts of interest:
Worked on short-term contracts at WHO on TB education

DOTs stands for directly observed therapy short course, the curative treatment for tuberculosis. At its core, it involves supervising the patient's swallowing of medication. One cannot have DOTs, however, without a coordinated program with the following components: reliable, widely available smear microscopy diagnosis; an uninterrupted drug supply; recording and reporting of cases and outcome; and, most important, government commitment to assure that necessary resources are available to maintain the program.[1] These 5 elements make up the DOTs strategy, adopted by the World Health Organization, that cures 85% of patients with tuberculosis. Two-thirds of the world's population has no access to DOTs programs.

In high-income countries, discussion about DOTs involves the pros and cons of supervised therapy and whether the 5% of noncompliant patients have a right to refuse treatment. Elsewhere the debate involves how to make the DOTs strategy available to more than the 16% of people who currently have access.[2-5] This discussion asks the far more important question: Does the estimated one-third of the world population, including 6.69 million tuberculosis patients who currently have no access to the DOTs strategy, have a right to expect it?[5]

> Studies show that DOTs produces higher treatment completion rates, reduces resistance, results in less need for retreatment and, overall, lowers the rate of tuberculosis.

It was long ago recognized that treatment had to be supervised, as shown in the early British Medical Research Council trials[6,7] and as vigorously promoted by the Denver TB outpatient clinic.[8] The melding of the 5 elements into a national TB program took place in Tanzania in a partnership between that government, Karel Styblo, and the International Union Against Tuberculosis and Lung Disease.[9] The subsequent adoption and marketing of the DOTs strategy by WHO and the efforts of the International Union Against Tuberculosis and the Royal Netherlands Tuberculosis Association have increased to over 100 the number of countries committed to the DOTs strategy and have increased the number of cases covered by the strategy to over a million.[2,4]

Noncompliance by doctors or patients with the standard 6-month treatment regimen is the commonest cause of treatment failure.[10,11] Studies show that DOTs produces higher treatment completion rates, reduces resistance, results in less need for retreatment and, overall, lowers the rate of tuberculosis.[12] Debate continues over selective versus universal application of DOTs. In favor of its universal application is the argument that determination of nonadherence is fraught with difficulty.[13] Those who use selective criteria apply social factors such as homelessness and unemployment, or the medical imperative of drug resistance, claiming that universal DOTs would be labor intensive, expensive, and unnecessary.[12] Those who advocate universal application of the strategy show that reallocation of resources achieves savings over the costs of failed treatment, spread of disease, and drug resistance.[12]

The legal arguments supporting the right to refuse treatment are negated by the need to protect the public's health from tuberculosis, which is spread to innocent bystanders in the air.[14] In 1993, the New York City Code of Health was amended to empower the commissioner of health to compel a person to be examined for suspected tuberculosis, to receive treatment for tuberculosis, or to be detained for treatment. Only 4% of 8000 patients who failed to adhere to DOTs in the community had to be detained for treatment. The graduated application of coersive measures, as well as the right of appeal, must be shown before resorting to confinement for treatment.[15] The right to refuse treatment is excepted in tuberculosis, however, because of its airborne transmission, DNA fingerprint evidence of casual spread, and the emergence of multidrug-resistant tuberculosis after poor treatment. The ethical right to detain to prevent transmission of infection is also supported in biblical and Talmudic law.[16]

In high-income countries, rates of tuberculosis are low and good outcome after treatment is assumed. But as in New York City in the 1980s,[10] unless surveillance is maintained, complacency can lead to a poor outcome. Therefore, in 1993 the US Advisory Council for the Elimination of Tuberculosis recommended directly observed therapy if completion rates were less than 90%. In that year, 34% received DOTs and 91.2% of them completed treatment.[17] In Canada, although DOTs is recommended,[18] its application varies from one province to the next.

The World Health Organization maintains a worldwide surveillance system of the application of the DOTs strategy, measuring indicators for each of the 5 components. The 1999 global tuberculosis report of 1997 cases[4]

identified 102 "DOTs countries" but only 59 with implementation throughout. Overall, 173 countries reported cases, for a total of 3.37 million or 37% detected of the 7.96 million estimated. Only 16% of the estimated number of smear-positive cases were reported from DOTs strategy programs. Where these programs exist, cure rates usually exceed the global target of 85%, but the case detection rate is well below the target of 70%.[4] There is a trend toward improved cure and detection rates in the 22 high-burden countries, which have 80% of the cases, but few reach the global targets.

The debate over the right of the 5% of people with tuberculosis to refuse DOTs must not distract us from the larger human rights issue that one third of the world's population has no access to the DOTs strategy.

Some remarkable successes have been achieved. In Bangladesh and Peru, for example, the implementation of the DOTs strategy has expanded rapidly and cured over 85% of the people treated.[4] In sub-Saharan Africa, however, in spite of well-executed countrywide programs, rates continue to rise through HIV/tuberculosis coinfection. Here the strategy cannot contain the rising rates but can prevent the emergence of untreatable drug-resistant disease.[19]

The debate over the right of 5% of people with tuberculosis to refuse DOTs must not distract us from the larger human rights issue that one third of the world's population[2] has no access to the DOTs strategy. Although the world's nations declared "Health for all by the year 2000" as the goal of the Alma Ata Primary Health Conference of 1978,[20] the entrenched inequalities between rich and poor countries and communities within them make equal access to the DOTs strategy unattainable. WHO's new director-general, Gro Harlen Brundtland, addressing the African region of WHO in April 1999, noted the uneven burden of disease, with 90% occurring in regions having 10% of the resources. Brundtland asked for partners in a "new universalism," assuring access to quality care.[21] This is the bioethical challenge of tuberculosis: to give to the 6.69 million tuberculosis cases who now have no access to the DOTs strategy the right to accept or refuse it.

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Proposed revisions to the Declaration of Helsinki

Paving the way for globalization in research

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A front-page article in the New York Times in June described a horrifying scenario: Cornell University researchers, using National Institutes of Health (NIH) funds, have followed dozens of Haitians infected with the HIV for years without providing the protease inhibitors and other medications that have revolutionized the care of patients with HIV.[1] The researchers actually turned down an offer of free medication from the French government. This study was in clear contravention of the 1996 Declaration of Helsinki, which requires that "In any medical study, every patient...should be assured of the best proven diagnostic and therapeutic method."[2]

For decades, the Declaration has provided an internationally accepted yardstick by which the ethical nature of research can be judged. But the research industry has mounted a coordinated, multipronged assault on these principles, endangering the health of research participants, particularly poor people and those in developing countries. In a revised draft considered by the World Medical Association, the phrase "that would otherwise be available to him or her" was appended to the principle quoted above.[3] This would open up the entire developing world (and, potentially, poorer sectors of the industrialized world) to research protocols that would be deemed unacceptable in the United States. The draft also permits the use of placebos if the outcome of interest is not "death or disability," regardless of the existence of effective therapy. Although not adopted, this draft articulates where the research industry hopes the Declaration will go.

This is just the first prong of the assault. Reacting to a 1997 controversy over the failure of US government-funded researchers to provide zidovudine to all HIV-positive pregnant women in vertical transmission studies in Africa and Asia,[4,5] researchers recently released a so-called consensus statement on future HIV perinatal research. Despite the demonstrated effectiveness of short (and hence substantially less expensive) courses of antiretroviral agents in reducing perinatal HIV transmission in developing world settings, the researchers concluded that in future studies "a no-intervention controlled design may be ethically justified in host countries where there is no antiretroviral therapy currently available."[6]

The next prong comes from the Joint United Nations Programme on HIV/AIDS, which has been developing ethical guidelines for the conduct of HIV vaccine trials. After lengthy consultation and meetings on 5 continents, no consensus was reached on several key issues.[7] UNAIDS is now poised simply to release the document as a UNAIDS policy document. That document will likely be based on a previous draft[8] that would also permit suboptimal treatment of participants who became HIV-infected during the trial, even though the researchers plan to follow such individuals prospectively for years.

Finally, the Council of International Organizations for Medical Sciences (CIOMS)[9] document is also undergoing revision, and the most recent version is said to recommend changes similar to those proposed for the Declaration of Helsinki, although the CIOMS draft has not circulated beyond the working committee.

To date, the efforts to dilute accepted ethical principles have featured academic or government scientists prominently; the pharmaceutical industry has remained safely offstage. If these changes are enacted, the pharmaceutical companies and their colleagues in the world of human experimentation corporations (formerly contract-research organizations) will be among the first to exploit the opportunity offered by enhanced access to "drug-naive"[10] patients, a descriptor used (in a possibly unintended double entendre) on the website of Quintiles, an international clinical trials firm. These organized assaults come at a propitious time: improvements in communication and transportation make research in developing countries more practical than ever. They are the ethical equivalents of the deregulation, low wages, exploitative working conditions, and reduced environmental protections that are the inevitable consequence of globalization. Where Nike leads, must the NIH follow?

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Mail

Thoughts from an emergency room, Littleton, Colorado

Michael Ament spent the month of April in Denver, Colorado, completing an elective in emergency medicine. Suddenly, all of Denver was facing an enormous emergency: 12 students shot dead at a Columbine High School in the Denver suburb of Littleton. Dr. Ament wrote the following letter to friends and faculty at the State University of New York, his medical school in Buffalo, New York. He is now an intern at the University of Colorado Health Sciences Center, Denver, and will begin his residency in neurology next year.

To the Editors,

The afternoon of the shooting, ironically, I was not scheduled to work in Emergency. I was approaching my last day—my last 10 hours—of medical school. When my wife, Julie, and I heard about the shootings, we reacted like everyone else in the community—with shock, a sense of helplessness, and a deep need to do something.

Julie and I did what many others did. We went to the Light of the World Catholic Church, where the survivors were gathered, and we helped. Nothing glamorous, just setting up tables, chairs, food, drink; pointing the way to the restrooms; and coordinating donations. At least it was something. It could never be enough.

Perhaps part of the lesson is that there is always room for unconditional love; there is always hope in a new beginning.

The next day, support gathered and became more organized. As the students and their families grieved, there was less and less for strangers to do, and yet the pain was greater and greater. Our small contribution was to arrange for the Colorado Humane Society to bring out the puppies.

The reaction, frankly, was stunning. Children and adults alike cuddled and played with the puppies. More tears than I've ever seen. These little animals provided what so many people with so much talk could not—a crack in the armor and a chance for catharsis.

Perhaps part of the lesson is that there is always room for unconditional love; there is always hope in a new beginning. That was a pretty good lesson to learn on my last day of formal medical education.

The community of Denver pulled together in one of the most fantastic displays of compassion and action that anyone could ever imagine. And amidst the anguish, we have seen more acts of selflessness, heroism, and kindness than we ever imagined possible. Many have been broadcast on the news, but many others occurred without fanfare: one person at a time, helping one person at a time, over and over and over.

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Med.Pix

Skin lesions with white rings

QUESTION: What are the cause and diagnosis of the hypopigmented areas seen around the pigmented lesions in Figures 1 and 2? (Both hyperpigmented areas are approximately 5 to 8 mm in diameter.)

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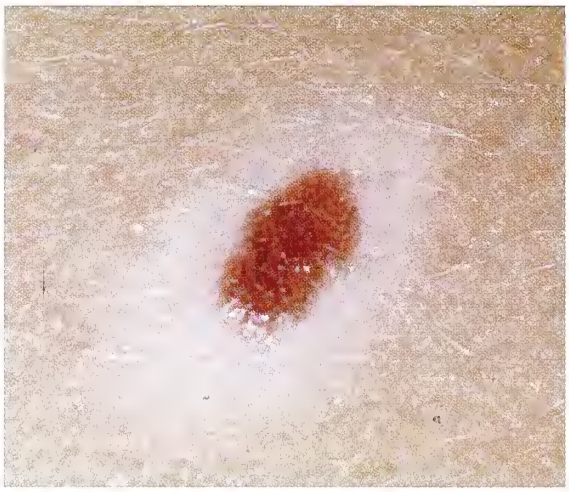

Figure 1 *Back*

Figure 2 *Upper chest*

ANSWER: The lesions in Figures 1 and 2 are halo nevi. These photographs were taken of halo nevi from two different young women. Both nevi were found on the trunk. They were noted incidentally during physical exams. Neither patient was symptomatic. Figure 3 shows a larger area of the back of the young woman pictured in Figure 1 with a cluster of halo nevi in various different stages. The patient in Figure 2 had a single halo nevus only.

Epidemiology

Halo nevi are principally found on the trunk and may be seen more commonly in adolescents, children, and young adults. A correlation with vitiligo has been reported.[1]

Mechanism

The halo nevus is a curious phenomenon in which there is an immunologic reaction around a nevocellular nevus (a nevus with nevus cells). The depigmented ring is caused by the destruction of melanocytes. Evidence points to the involvement of CD8+ T cells as the potential effectors in the destruction of these melanocytes.[2] The mechanisms responsible for the halo nevus present an interesting link with the immune response to melanoma.[2] Although it has been reported that halo nevi are found in correlation with melanoma at distant sites, there is no firm evidence to support anything but a coincidental link between melanoma and halo nevi.

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Note: If the patient's identity is recognizable, a signed permission form should accompany the submission materials.

Figure 3

Courtesy of Lazarus R, May R, Tabinck E, Siegel D. Skin surgery: a practical guide. St. Louis: Mosby-Year Book, Inc.; 1998.

Figure 4

Three stages of the halo nevus (stages 1 and 2 are seen in Figure 3):

1) A white halo develops around the normal brown pigmentation of a benign nevocellular nevus (months).

2) The halo nevus may then progress to a complete loss of pigment, with only the remaining halo visible (months to years).

3) Repigmentation of halo (months to years).[1]

Differential diagnosis

Mooney and colleagues examined the pathology of 142 lesions that were given the clinical or histologic diagnosis of halo nevus. All but 3 were found to be compound, junctional, or intradermal nevi with a broad spectrum of atypia.[3] The halo phenomenon occurs in a wide spectrum of skin lesions, including melanoma, blue nevi, Spitz juvenile nevi, dermatofibroma, and neurofibroma.[1] Halos may also occur around basal cell carcinomas and congenital nevi.[4] Therefore a lesion with a halo should not be regarded as a single clinical or pathological entity. The central lesion should be evaluated and biopsied if there is a suspicion of skin malignancy.

For example, Figure 4 shows a basal cell carcinoma (BCC) with a surrounding halo. The central lesion is a very typical-appearing nodular BCC, with a pearly-white, smooth appearance showing telangiectasias and a loss of the normal pore pattern. Biopsy confirmed the diagnosis of BCC, and the lesion was fully excised with appropriate margins.

Although melanomas can show regression of pigmentation, these lighter areas are irregular and asymmetric. Melanomas that appear to have a halo tend to have an asymmetric halo, and the central pigmented lesion shows a number of the ABCDE criteria (see box). In contradistinction, the usual benign halo nevus tends to a very symmetrical hypopigmented ring around an evenly pigmented, benign-appearing nevus.

Treatment

If a halo nevus appears suspicious for a basal cell carcinoma or a melanoma, it is essential to biopsy the central lesion. Benign-appearing halo nevi as seen in Figures 1 to 3 do not require biopsy. The treatment for both patients in Figures 1 to 3 is reassurance and observation. Any suspicious changes in the central lesion in years to come might prompt a future biopsy.

ABCDE guidelines for diagnosis of melanoma

- **Asymmetry:** Benign nevi are symmetrical; melanomas tend to have pronounced asymmetry.
- **Border:** Benign lesions usually have smooth borders; melanomas tend to have notched, irregular outlines.
- **Color:** Benign lesions usually contain only one color; melanomas frequently have variegated color.
- **Diameter:** Benign pigmented lesions are usually smaller than 6 mm in diameter.
- **Elevation:** A malignant melanoma is almost always elevated, at least in part, so that it is palpable.

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Original Research

Hospitalizations for injury among American Indian youth in Washington

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ABSTRACT ● **Objective** To determine the rate and causes of hospitalization for injury among American Indian and Alaska Native (AI/AN) youth in Washington compared with youth of all races. ● **Methods** Subjects were aged 0 to19 years and were admitted to civilian hospitals for care of an injury (International Classification of Diseases N codes 800-995) in Washington between 1990 and 1994. Deaths occurring in the pre-hospital setting and emergency department were not included. Using several fields of identifying information, the Washington state hospital discharge database was linked with the Indian Health Service (IHS) patient registration database to identify AI/AN youth. Denominator data included the total age-specific IHS user population for American Indians and population estimates derived from the US Census. Incidence ratios (IRs) were calculated to compare rates of hospitalization between AI/AN youth and all youth in Washington. ● **Results** A total of 694 hospitalizations for injury were identified for AI/AN youth and 29,048 were identified for all races. The rate of hospitalization for injuries among AI/AN youth was 507 discharges per 100,000 youth (IR = 1.30; 95% confidence interval [CI] 1.20 to 1.40). The leading mechanism of injury was motor vehicles (IR 1.73, 95% CI 1.49 to 2.01), which was followed by falls (IR 0.95, 95% CI 0.79 to 1.15) and poisonings (IR 1.20, 95% CI 0.80 to 1.78). The disparity was greater for intentional injuries (IR 1.71, 95% CI 1.44 to 2.04). The highest IR for all unintentional injuries was for injuries from fire (IR 2.35, 95% CI 1.42 to 3.87). AI/AN children aged 15 to 19 had the greatest disparity for rates of injury hospitalization (IR 1.4, 95% CI 1.25 to 1.56). ● **Conclusion** AI/AN youth in Washington had a higher rate of hospitalization for injury compared with all youth in the state. Disparities were greatest for injuries related to motor vehicles and assaults. When linked, hospital discharge data can be used for surveillance of AI/AN hospitalizations.

INTRODUCTION

Injuries are a leading cause of childhood morbidity and mortality throughout the world. Although there have been substantial declines in the rates of death from injuries among children in developed nations, injuries remain the principal threat to the health and welfare of children and adolescents.[1] Rates of injuries are known to be higher among indigenous peoples in North America, Australia, and New Zealand.[2-7] In the United States, American Indians and Alaska Natives (AI/ANs) have higher rates of injury morbidity and mortality than other races.[8] Hospitalization rates for injury among AI/ANs have been published for the Indian Health Service (IHS) service population, but these analyses have not specifically focused on children.[9] Furthermore, these analyses have used IHS hospital discharge data and may miss AI/AN patients who receive hospital care outside of the IHS system, especially if the payer is other than the IHS. State hospital discharge registries represent another potential source of data for surveillance of hospitalizations, but many do not contain racial or ethnic identification data. If they do, the potential also exists for racial misclassification.[10]

The severity and cost of injury hospitalizations for AI/ANs have not been well described. In many areas, where IHS hospitals care for most hospitalized patients, there is no billing for registered AI/ANs; therefore, no charges or costs are calculated. Only those patients receiving care in contracted health facilities outside of the IHS system (often the most severely injured) receive a bill. As Indian tribes and Native corporations assume more responsibility for their health care under self-determination laws, leading to fixed government contracts, most hospitalization costs will be borne directly by tribes.[11] As a result, tribes will have an increasing financial incentive to reduce preventable injuries and illnesses among their membership, and local surveillance mechanisms using available data will be essential.

The purpose of this study was to determine the incidence of hospitalization for injuries among IHS-eligi-

ble AI/AN youth in Washington state for the years 1990 to 1994. By linking state hospital discharge and IHS patient registration data, we sought to compare injury hospitalization rates within this group with those of the state's entire youth population. Finally, we sought to determine the severity and total costs of these injuries.

METHODS

Sources of data

The Comprehensive Hospital Abstract Reporting System (CHARS), the state hospital discharge registry, contains a record for each individual discharged from a civilian hospital in Washington state. Included in the database is information on patient characteristics, such as age, sex, type of injury, mechanism of injury, length of hospital stay, intent of injury, cost of hospitalization, and payer. CHARS does not contain ethnic or racial identifying information.

The IHS is charged with providing direct and contracted healthcare services to enrolled members of federally recognized tribes and maintains a database of members who are registered for IHS services. There are no inpatient IHS facilities in Washington state; all inpatient care is provided in private hospitals under contract with the IHS or the tribe. Since the CHARS database does not contain information on race or ethnicity, AI/AN race was assessed using the IHS patient registry. The registry includes the patient's full name (including alias names), address, date of birth, and sex. The IHS patient registration file was linked to the CHARS database to determine which individuals hospitalized for injury were of American Indian or Alaska Native origin.

We used a computerized matching program to link the Washington state hospital discharge database with the IHS database, using the first 2 initials of the patient's first and last names, sex, and date of birth. Alias names, when present, were also used for possible matching. Only exact matches on all fields were allowed.

Study population

The numerator consisted of all IHS-enrolled children and adolescents (aged 0 to 19 years) who linked to the CHARS database for the years 1990 to 1994, with a principal diagnosis of injury (International Classification of Diseases, 9th revision [ICD-9] CM N codes 800-995) averaged annually over the 5-year period. The denominator for American Indian children included all IHS-enrolled members aged 0 to 19 reported to be living in Washington state at the study mid-point in June 1992.

Rates of hospitalization for injuries among AI/AN youth were compared with those of all youth in the state, using the statewide hospital discharge database. The denominator used for all youth in the state was the State of Washington Office of Financial Management's intercensal population estimate of 0-to-19-year-olds residing in Washington in 1992, the mid-point of the study. The injury severity score,[12] a widely recognized tool to characterize anatomic injury severity, was derived for each subject using ICDMAP, a computerized program that converts ICD-9-CM-coded diagnoses into abbreviated injury scale scores and composite injury severity scores. The abbreviated injury scale quantifies the extent of injury to each of 6 body regions. The injury severity score is computed by summing the squares of the 3 highest abbreviated injury scale scores in the 3 body regions with the highest abbreviated injury scale scores. An injury severity score greater than 15 is considered to represent a severe injury; scores of 9 to 15 represent moderate severity.[12]

External cause of injury codes (ICD-9-CM E codes) included in the hospital discharge database were categorized as proposed by the Centers for Disease Control and Prevention, with modifications to stratify more of the mechanisms grouped as "other."[13] We excluded the following E codes related to adverse effects of care: E870-6, E878-9, E930-49.9, E929, E959, E969, E977, E989, and E999. Mechanisms of injury (E codes) were available for 659 (92.2%) AI/AN hospitalizations and for 27,668 (95.2%) all-race hospitalizations.

Charges in the discharge database were used as a proxy for cost and reflected charges only for hospital care; prehospital charges and professional fees were excluded.

Table 1 *Hospitalization rates for unintentional injuries in youth (expressed as hospital discharges/100,000 youth) by mechanism, Washington state, 1990-1994*

Mechanism of injury	AI/AN	All races	Incidence ratio (95% CI)
Motor vehicles:			
Traffic-related	127.8	73.9	1.73 (1.49 to 2.01)
Pedal cyclist	16.1	14.2	1.13 (0.74 to 1.72)
Nontraffic	9.5	8.7	1.10 (0.63 to 1.90)
Falls	79.6	83.5	0.95 (0.79 to 1.15)
Struck by/against	27.8	26.5	1.05 (0.76 to 1.45)
Poisoning	18.3	15.3	1.20 (0.80 to 1.78)
Cut/pierced	13.9	11.2	1.24 (0.78 to 1.95)
Fire/flames	11.7	5.0	2.35 (1.42 to 3.87)
Hot object/scalding	10.2	10.7	0.96 (0.56 to 1.62)
Other transport	9.5	6.3	1.50 (0.87 to 2.60)
Environmental factors	6.6	7.9	0.83 (0.43 to 1.60)
Firearm	5.1	3.5	1.46 (0.69 to 3.10)
Suffocation	5.1	5.3	0.96 (0.46 to 2.03)
Machine	3.6	3.0	1.23 (0.51 to 2.99)
Total	**373.2**	**313.8**	**1.19 (1.09 to 1.30)**

RESULTS

Injury discharge rates

There were a total of 694 injury hospitalizations among AI/AN youth and 29,048 among all youth residing in

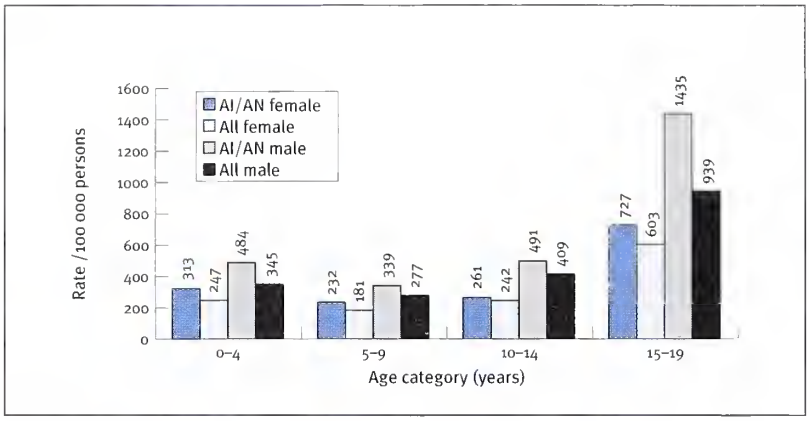

Figure 1 *Youth injury hospitalization rates by age, sex, and race*

Washington between 1990 and 1994. The population of IHS-enrolled 0-to-19-year-old AI/ANs was estimated at 26,659. According to census data, 34,736 AI/AN youth and 1,485,863 0-to-19-year-old youth of all races resided in Washington in 1992.

Although IHS-enrolled youth make up 1.8% of Washington's youth population, they represented 2.4% of injury hospitalizations. AI/AN youth had an annualized injury hospitalization rate of 507/100,000 population compared with 391/100,000 for all youth statewide (incidence ratio [IR] 1.30, 95% confidence interval [CI] 1.20 to 1.40). The disparity between groups was considerably lower for unintentional injuries (IR 1.19, 95% CI 1.09 to 1.30) than for intentional injuries (IR 1.71, 95% CI 1.44 to 2.44).

The highest rates of injury hospitalization occurred among AI/AN males aged 15 to 19 years (1435/100,000 population). Although 15-to-19-year-old AI/AN males compose 22% of the AI/AN youth population, 45% of AI/AN hospitalizations occurred in this group. When stratified by age and sex, AI/ANs appeared to have consistently higher rates of injury hospitalization in every group (Figure 1).

Hospitalizations for unintentional injury among AI/ANs most frequently followed motor vehicle injuries (26% of admissions), falls (17%), and poisonings (12%). Falls were the leading mechanism (22%) among all Washington youth, followed by motor vehicles (19%) and poisoning (12%) (Table 1). AI/AN males were more than 1.5 times more likely to be hospitalized for motor vehicle occupant injuries than females and more than 4 times as likely to be hospitalized for motorcycle injuries. Among unintentional injuries, the greatest incidence ratio was for injuries related to fire and flames (IR 2.35, 95% CI 1.42 to 3.87).

Rates of intentional injuries and assaults were higher among AI/ANs compared with all youth (IR 1.71, 95% CI 1.44 to 2.04) (Table 2). The greatest disparity in rates for AI/ANs, compared with the state as a whole, was for assaultive injuries. Incidence ratios for self-inflicted injuries were about half of those for assaults. AI/AN males were nearly twice as likely to be hospitalized for intentional injuries and nearly 5 times as likely to be hospitalized for assault-related injuries compared with AI/AN females. AI/AN females were more than twice as likely, however, to be hospitalized for self-inflicted injuries than their male counterparts. The leading mechanism of self-inflicted injury was poisoning (75%), followed by cutting or piercing (10%). The most frequently reported mechanisms in assault hospitalizations were being struck (28.2%), child battering/maltreatment (25.4%), and firearms (19.7%).

During the 5-year study period, 10 injury hospitalizations resulted in death among AI/AN youth after admission, 8 of those related to motor vehicles. Poisoning was the mechanism for 1 in-hospital death, and 1 cause of death was unspecified. Seven of the deaths were in the 15-to-19 age category.

Despite higher rates of injury hospitalizations among AI/AN youth, we found no significant differences between the mean injury severity score or length of stay between the 2 groups (AI/AN 8.4 vs state 8.5). AI/AN males had a significantly higher mean injury severity score compared with females (male 9.2 vs female 6.9, P=0.018). There were no other significant differences within the AI/AN group or between groups.

Hospital charges during the 5-year study period for the 694 AI/AN injury hospitalizations totaled $5,113,733. The mean and median charges per injury hospitalization were $7356 and $4142.93, respectively, and did not differ substantially between the 2 groups.

Motor vehicle injuries led to the highest cumulative charges ($1,560,739.80), with a mean charge per case of $9180. Injury by fire and flames had the second highest 5-year total charge ($643,353) but the highest mean charge at $37,844. Total charges for fall-related injuries were $500,000, with a mean of $4526.

Medicaid was the leading primary payer of hospital charges, accounting for half of the AI/AN hospitalizations, followed by private insurance (28%) and the IHS (11.2%). Among all youth, private insurance was the primary payer for 31% of the hospitalizations, followed by Medicaid (22%) and healthcare service contractors (19.5%).

DISCUSSION

Our study found that AI/AN youth in Washington state have a significantly higher rate of injury-related hospitalization when compared with all youth in Washington state. This disparity seems to be related to a few key mechanisms of injury: intentional, fire-related, and motor vehicle occupant injuries.

Motor vehicle injuries were the most prominent cause of injury hospitalizations among AI/AN youth but ranked second for all youth in the state. Other studies using hospital discharge data have also found falls to be the leading cause for all youth, with motor vehicles the leading mechanism only among 15-to-19-year-olds.[14-16] One other population-based study of childhood injuries in an American Indian community also showed that motor vehicles are the leading cause of hospitalization for AI/AN youth, followed by falls.[17] Although few studies have compared injury discharge rates among racial and ethnic groups,[18,19] we are unaware of any other large, detailed, population-based studies that have compared the injury-related hospital discharge rates of AI/AN youth with those of the youth of any other ethnic groups.

Variations in rates of injury among population groups are likely to be related to disproportionate differences in known risk factors. For example, a study on residential house fires in one Native community reported a high prevalence of risk factors such as smoking combined with alcohol, smoking in bed, and using wood stoves.[20] A study of risk factors for motor vehicle injury using a statewide traffic accident database linked to the IHS database concluded that AI/AN drivers involved in rural crashes were much less likely to be wearing seat belts and more likely to be alcohol-impaired at the time of a crash than non-Indian drivers involved in rural crashes.[21] Other studies have also confirmed the prominent role of alcohol in motor vehicle injuries among American Indians.[22,23]

The comparatively limited role of the IHS as the primary payer for AI/AN hospitalizations reflects several factors. The IHS and tribes will usually seek other third-party financing for medical care before using their own contract funds for hospital care. Since the IHS considers itself as the payer of last resort, private payment or Medicaid is used first if possible. In many other areas of the United States, where the IHS is providing direct inpatient care, much of the cost is borne by the IHS.

Limitations

Hospital discharge databases have some limitations for injury surveillance. They have a comparatively limited scope of clinical detail, may have inconsistent E coding, and may double-count patients transferred or readmitted for the same injury.[24] In addition, this type of database only provides information on injuries requiring hospitalization and excludes deaths from injuries that occurred at the scene or in the emergency department.

Another potential limitation of this study is that the use of IHS eligibility as a measure of AI/AN ethnicity is likely to underestimate the total population of AI/AN youths who are hospitalized. Many who identify themselves as AI/AN are not enrolled in the IHS because they never enrolled or because they are ineligible for services. American Indians living in urban areas are less likely to be enrolled in the IHS because benefits may not be portable if they are not living on or near their tribal homes. These facts may have meant that our study population included a disproportionate number of rural Indians.

Table 2 *Hospitalization rates for intentional injuries in youth (expressed as hospital discharges/ 100,000 youth) by mechanism, Washington state, 1990-1994*

Mechanism of injury	AI/AN	All races	Incidence ratio (95% CI)
Self-inflicted injuries:			
All mechanisms	42.4	35.5	1.19 (0.92 to 1.55)
Cut/pierced	4.4	2.8	1.58 (0.70 to 3.56)
Poisoning	32.1	30.5	1.05 (0.78 to 1.42)
Assaults:			
All mechanisms	51.1	19.1	2.67 (2.10 to 3.40)
Struck by/against	14.6	6.6	2.22 (1.42 to 3.47)
Child maltreatment	13.1	4.0	3.37 (2.09 to 5.42)
Firearm	10.2	3.9	2.58 (1.51 to 4.42)
Cut/pierced	5.8	2.9	2.03 (1.00 to 4.11)
Total	**93.5**	**54.6**	**1.71 (1.44 to 2.04)**

Although these general patterns of injury may be consistent with other studies, we recognize that important variations in the epidemiology of disease and injury exist among IHS service areas and that our findings may not be generalizable to other regions of North America or to other international indigenous groups.[25]

We believe that a strength of this study is the novel linkage of IHS enrollment files to state hospital discharge databases to ascertain the epidemiology of hospitalizations. This may prove to be an important tool for the future, as analysts attempt to refine their definitions of the epidemiology of illness and injury among AI/AN youth.

Prevention programs

Begun in 1982, the IHS injury prevention program has assisted Indian communities with the development of injury prevention strategies.[26] In 1990, Congress began appropriating funds to the 12 IHS areas, specifically earmarking them for injury prevention programs and training. Despite the huge burden of injury on the health of AI/ANs, injury prevention constitutes a very small proportion of funds in the IHS budget.

The passage of the Indian Self-Determination and Education Assistance Act (PL 93-638) in 1976 led to the current trends of tribes' taking responsibility for operating their own healthcare organizations and the parallel devolution of the IHS.[27] Tribal leaders will need to be informed of the epidemiology of injury in their communities as well as of effective available strategies for

primary prevention and control. The unique information obtained from the linkage of databases, as shown in this study, can ultimately be useful toward these ends.

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COMMENTARY

A combination of traditional wisdom and public health could help

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Although this paper concludes that Native American children and youth in Washington state have higher rates of several types of injury, the authors are careful to point out that the situation in one state cannot be generalized to other parts of the country. There are, after all, more than 500 federally recognized tribes, each with its own culture, geography, and socioeconomic circumstances. Other articles, many cited by the authors, do confirm that the problem is not unique to the Pacific Northwest.

Why might Native American youth be at greater risk from such injuries as assaults, motor vehicle crashes, and house fires? Trained in the public health model, injury prevention experts (including this study's authors) look to "disproportionate differences in known risk factors." For example, higher rates of cigarette smoking and alcohol use are known risk factors for deaths due to house fires. Reducing these risk factors—by raising taxes on alcohol and cigarettes, for example—is an approach that emerges directly from the public health model.

Native American communities have their own approaches to analyzing and addressing such problems. How might a hypothetical "National Council of Indian Elders" discuss the question of increased injuries among Indian youth? Of course, there would be a great deal of diversity among both the individual elders and their tribes. They would also have a great deal in common, however,

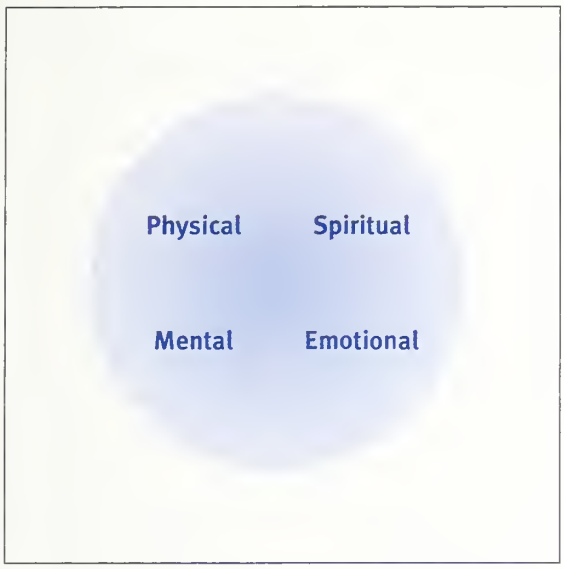

Figure 1 *The concept of the four directions is shared by many Native American communities. The circle denotes inclusiveness, unity, and harmony.*

with virtually everyone expressing the importance of the four directions, emphasizing their connection with nature and the land, and interpreting disease as a result of life out of balance.

Questions the elders would ask

Rather than using the Haddon Matrix (a public health model consisting of 3 factors—host, agent, environment—and 3 phases—pre-event, event, and post-event) to analyze the problem, the elders might use a circle divided into quadrants (see Figure 1). One circle might emphasize the individual, family, community, and world at large; another circle would highlight the physical, mental, emotional, and spiritual realms. The elders would likely ask, "What is happening in our families, our communities, and the world at large that leads many young people to drink alcohol, to have violent anger, to be so despairing that they attempt to end their lives? In what ways has life gone out of balance for our youth, so that connections to self, family, community, and the land are no longer harmonious?" At some point, several young people might be invited to join the circle of elders to help answer these questions.

What strategies would emerge? Proposed solutions would emphasize traditional values and approaches. There might be an effort to encourage young people to participate in healing ceremonies. Grossman has previously described Spirit Dancing as a cure for Spirit Sickness (probably a form of depression) among youth in a Salish Indian community.[1] In an approach that combines physical, emotional, and spiritual elements, the elders might urge tribal leaders to initiate a program of summer employment for youth involving healing the land. (Remember the Civilian Conservation Corps, which helped America recover from a different kind of depression?) Young people would work together in planting trees, removing graffiti, and restoring polluted streams or damaged soil. Such a program could reduce youth violence by providing teens with an income, enhancing their self-esteem, teaching them to work collaboratively with peers and adults, and instilling traditional values about community and the environment. Another example of a program incorporating traditional values is the Comprehensive Adolescent Pregnancy and Parenting program in Ganado, Arizona. This program offers teens family planning services and day care, involving Navajo grandmothers who model their tribal values in parenting and child care. After the initiation of this program, in 4 years, the number of teenage pregnancies at the Ganado High School fell from 35 to 2.[2] Would anyone doubt a favorable impact of this program on incidents of child abuse and neglect?

Conclusions

Both traditional wisdom and the public health model have much to offer in addressing high rates of injury among Indian youth. There is no need to take an either-or approach: the challenges of balancing life in 2 worlds, Native and non-Native, are familiar to Native American people.[3] The vision of health as encompassing mind, body, and spirit—operating not just at the level of the individual, but also involving family, community, and society—is one that all of us might benefit by embracing.

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capsule

Protecting Kids from Strep Pneumonia We can't prevent invasive infection and have limited data on modifiable risk factors, but a case control study in Pediatrics (1999; 103:28) suggests meningitis and other severe infections are linked with attendance at day care centers. For children under one, bottle feeding was also a risk factor, as was a recent course of antibiotics in children between the ages of one and two.

Household poisoning exposure among children of Mexican-born mothers: an ethnographic study

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ABSTRACT **Objective** To explore reasons for high rates of unintentional poisoning among Latino children under 5 years old. **Design** Ethnographic interviews were carried out using a sample of mothers identified via door-to-door canvassing in an area with documented high injury rates among Latino children. Interviews included many open-ended and follow-up questions to elicit a detailed family history and emphasized observation of conditions and behaviors in the homes. **Setting** Low-income neighborhoods of Southern California. **Subjects** Fifty mothers born in Mexico with children under 5 years old. **Results** Children were exposed to potential poisoning agents in more than 80% of homes. Contributory factors related to culture included favorable attitudes toward iron as a healthful substance; extensive use of products that lack child-resistant packaging, such as rubbing alcohol and medicines from Mexico; high prevalence of shared housing; limited familiarity with toxic household chemicals not widely used in Mexico; and inability to read warning labels in English. **Conclusion** Current Poison Control Center outreach efforts should be expanded. Clinicians are uniquely positioned to advise parents about the safe use and storage of toxic substances, including widely used products lacking child-resistant packaging. Medicines should be labeled in Spanish for those who do not know English.

INTRODUCTION

Unintentional poisoning is common among young children nationwide.[1] In California, poisoning is second only to falls as a cause of serious injury in children under 5 years old.[2] Studies suggest that Latinos—expected to be the largest minority group in the United States by 2005[3]—are at increased risk of poisoning. In New Mexico, poison-related mortality rates for Hispanic children aged 0 to 4 years were about 15% higher than for non-Hispanic whites.[4] In Southern California, Agran et al.[5] found that Hispanic (mainly Mexican) children were more than twice as likely as non-Hispanic white children to be hospitalized for poisoning, even after adjusting for census-block group, a proxy for socioeconomic status. Anderson et al.[6] hypothesized that cultural and environmental transitions associated with a move to the United States may increase risk.

Data collected but not published by Agran et al.[5] indicate that cultural factors and/or unfamiliarity with US medicines and chemicals may be important. Of 52 Hispanic children hospitalized for poisoning, 12 had been poisoned by iron supplements or multivitamins with iron. One infant had been treated with a dangerous lead compound (*azarcón*) brought from Mexico,[7] where it is commonly used for a stomach ailment known as *empacho*. Another infant had been given a preparation by mouth that was intended to be mixed with water and used as a shampoo for head lice. Another was overcome by fumes from an insecticide bomb when he was brought back into the home too soon after the bomb was set off. Four children had ingested caustic substances, including oven cleaner, drain opener, and wart remover. Five poisonings involved medicines manufactured in Mexico, none of which had child-resistant packaging.

To understand these findings, we searched the literature for articles on possible reasons for elevated rates of poisoning among Latino children. When we found none, we designed an ethnographic study to explore this issue. A recent task force report on the health of immigrant children, sponsored by the National Research Council and the Institute of Medicine,[8] states that in-depth ethnographic studies of household factors influencing health are essential for full understanding of statistics from broader surveys.

METHODS

Most Latinos in Southern California are of Mexican ancestry, so we focused our study on the children of mothers born in Mexico. Between July 1997 and June 1998, we interviewed 50 Mexican-born women who had at least one child under 5 years old, the age group at highest risk for unintentional poisoning.[5] Interviews took place in the mothers' own homes in 5 contiguous cities located about 40 miles south of Los Angeles: Santa Ana (17 women), Orange (14), Anaheim (9), Garden Grove (8), and Costa Mesa (2). These cities represented the geographical area where the epidemiological study documented high injury rates among Hispanic children.[5] Since the goal was to understand those findings, we carried out our ethnographic study in the same area. Census figures indicate that of the 910,000 people living there in 1990, about 40% were Hispanic.[9]

Within these cities, census block groups shown by the epidemiological study to have the greatest number of injuries were chosen. Mothers were identified via systematic door-to-door canvassing in each census block group. Among 55 women meeting the study criterion of having a child under 5 years old, 5 declined to participate. Mothers signed a consent form and were paid $20 for participating. The study was approved by our university's institutional review board.

A sample size of 50 was chosen. That number exceeds the 30 that anthropologists consider adequate for exploratory studies using qualitative methodology[10] yet is small enough to allow for extended questioning and observation. Each interview lasted 2 to 3 hours. Interviews were carried out by a medical anthropologist who spoke Spanish and had more than 2 decades of experience working with and writing about Mexican populations (the first author), accompanied by a bilingual, bicultural female research assistant of Mexican descent.

The method was ethnographic.[11] The goal was to understand pediatric injury from the mother's point of view; therefore, the interviews were not limited to a set of questions determined in advance. Although a semi-structured interview guide was used, it contained open-ended questions. Many follow-up questions were asked. As is customary in ethnographic studies, information gained from one mother was presented to the next for validation, then to the next, and so on. Mothers were interviewed in their preferred language, English or Spanish.

During the interviews, we took notes rather than using audiotapes. We also observed children's and mothers' behavior. We documented the presence of Mexican medicines and over-the-counter medicinal substances in the home and used a checklist to record how all medicines and household chemicals were stored. Since the ability to read English well is crucial for the safe use of medicines and household chemicals labeled in English, mothers were asked about their language competency. In questionable cases, mothers were tested by being asked to read from a simple pamphlet.

RESULTS

Sociodemographic data

Table 1 summarizes the demographic data. Mothers were living on very low incomes in extremely crowded households. The mean income per person was just over $300 a month. Three-quarters (38) of the women lived in residences shared with other families, and 84% lived in apartments. In 2 cases, 15 people were sharing a small 2-bedroom apartment. All mothers had television sets and 38 had access to a telephone in their home. A few had heard of Poison Control Centers, but none had a telephone number at hand. Only 14 could read any English, and of these, only 3 could read it well. One woman was interviewed in English and Spanish, the other 49 in Spanish.

Table 1 *Selected features of Mexican-born mothers and their households (n=50)*

Feature	Mean	Range
Age of mother (years)	28.3	19-43
Number of children	2.6	1-6
Number of children <5 years old	1.5	1-3
Mother's years of schooling	7.4	0-14
Mother's years in United States	7.3	<1-19
Monthly income of family	$1,337	$720-$2,600
People per room in dwelling	1.8	1.0-3.8
Families per dwelling	2.4	1-6

Two-thirds of the mothers (66%) had emigrated to the United States from Mexico's rural areas *(ranchos)* or small or medium-sized towns *(pueblos)*. They said that in these locales, medical care by doctors was minimal. Pharmacies did have a small selection of medicines, but because of poverty and cultural norms there was a heavy reliance on herbal preparations and other home remedies *(remedios caseros)*. Mothers also said that certain very hazardous household chemicals common in the United States, such as toilet-bowl cleaners containing hydrochloric acid, were unknown in Mexico outside the larger cities.

Storage of medicines and household chemicals

We considered that medicines and household chemicals were accessible to children if they were not stored "high and hidden." Items were judged accessible if they were stored in plain view in refrigerators, on open shelves or windowsills, on tables or countertops, on toilet tanks, in unlatched kitchen or bathroom base cabinets, in low drawers, in under-bed storage boxes, or on the floor. Items were judged not accessible if they were stored on high shelves in kitchen cabinets, on the tops of refrigerators, or in medicine cabinets, even though a determined child could reach them by climbing.

Very few families had stored all medicines safely. In the 50 households visited, a total of 56 containers of medicine or multivitamins with iron—9 lacking child-resistant packaging—were stored in places accessible to children. In 2 cases the child-resistant cap had been removed from the medicine container for the mother's convenience.

Safe storage of all household chemicals was also rare. The following chemicals were stored or located in places accessible to children: liquid bleach (32 homes), cleansing powder (28), rubbing alcohol (10), oven cleaner (8), insecticide spray (5), car-cleaning chemicals (4), lighter fluid (2), drain opener (1), and boric acid powder to repel roaches (1). The bleach, cleansing powder, rubbing alcohol, and boric acid powder did not have child-resistant

packaging, and 3 of the 4 cans of car-cleaning chemicals were missing their caps.

Overall, we found that only 10 families (20%) had stored all medicines and iron-containing vitamins safely, while only 9 (18%) had stored all household chemicals safely. Thus children were to a greater or lesser degree exposed to potential poisoning agents in more than 80% of the homes visited.

None of the mothers had functioning child-resistant latches on the kitchen and bathroom base cabinets, and 2 said they had never heard of such devices. Three had latches or makeshift ties for the knobs, such as a ponytail holder or shoelace, but the latch or tie was not fastened at the time of the interview, and in 1 such case the child was playing with the contents of the base cabinet. Two mothers had no latches but had taken the knobs off the cabinets to slow down the children's access. Several said that they had had latches, but they had broken with use.

Cultural factors underlying heightened exposure to poisons

Our study identified several culture-related factors affecting poisoning exposure among children of Mexican-born mothers.

First, attitudes toward iron were very favorable—so much so that iron supplements and iron-containing vitamins were sometimes stored with foods rather than medicines and were relatively accessible. We saw them in refrigerators, on pantry shelves, and in a desk drawer alongside herbs used to make medicinal tea. Many mothers said that iron-containing vitamins made children eat and weigh more, which they associated with good health. They expressed much concern about children being "too thin."

Second, there was substantial use of hazardous products lacking child-resistant packaging such as Mexican medicines, rubbing alcohol, and liquid bleach and cleansers. Five of the 50 mothers had Mexican medicines in their homes. When asked why people used such medicines, mothers said that they were almost always cheaper, and also more potent, than medicines from the United States. Several added that while US-born children of Mexican parents were covered by health insurance through Medicaid, adults were not and therefore might purchase Mexican medicines at shops and swap meets to avoid paying for a doctor visit. (Such purchases can be made fairly easily in urban areas of the United States with large Hispanic populations.)

Rubbing alcohol was observed in about half of the homes visited, and in 10 homes it was stored in an unsafe manner, typically on a nightstand or low table. It was used to treat aches and pains and the Hispanic folk disease known as *aire*. Toddlers' exposure to liquid bleach and cleansing powder was also very high. We observed that bleach, especially, was rarely stored in a secure place. Because the bottle was so big and frequently used, it was often left on the floor in plain view. On the day of the interview it was in active use in 5 homes, in 1 of which the bottle had been left open in a bathroom sink.

Another important cultural factor affecting poisoning exposure was the high prevalence of shared housing (76%). Different families often occupied different bedrooms in the same apartment or rental home. Mothers said that this was known as "living in a bedroom" and that safe storage of both medicines and household chemicals was difficult in such situations. Under such circumstances, people usually stored medicines and chemicals in their family's own bedroom, sometimes in places easily accessible to children. When we asked why so few families stored their medicines in a medicine cabinet, mothers said that families living in a bedroom did not do this because bathrooms were shared, and they did not want others using their things.

Further, people in shared quarters could not easily control how others stored hazardous substances. One mother complained—and we observed—that while she had her own household chemicals stored up high, another family in the apartment had its chemicals stored under the bathroom sink. Because about three fourths of the mothers shared their residence with other women of childbearing age, the likelihood of exposure to iron was great. In the 2 homes where grandparents were present, we saw their medicines left out in the open.

Lack of cultural familiarity had led some mothers to store caustic products in an unsafe manner. They felt that it was "modern" to use products such as oven cleaner and drain opener but did not recognize the hazards. Warning labels were written in English, which few mothers could read. We also discovered that about one third of the prescription medicines in the homes were labeled only in English.

DISCUSSION

Ethnographic findings presented here indicate that children of mothers born in Mexico who have low incomes are at high risk of unintentional poisoning. Observation in homes in an urban area of Southern California revealed that such children were exposed to unsafe storage of medicines and household chemicals in more than 80% of the 50 homes visited. Questioning of mothers revealed several contributory factors: favorable attitudes toward iron as a healthful substance; extensive use of products that lack child-resistant packaging, such as medicines from Mexico, rubbing alcohol, liquid bleach, and cleansing powder; high prevalence of housing shared with others, including groups likely to have potentially dangerous medicines, such as women of childbearing age who take iron and grandparents; and inability to read warning labels in English.

Our study was not designed to compare poisoning exposure among different ethnic groups or among Latino families of different socioeconomic status. Nor did it focus on maternal and child characteristics such as depression and impulsivity, which are implicated in pediatric poi-

soning.[12-17] Rather, as a first attempt to identify issues contributing to high rates of poisoning among low-income Latino children, we documented high levels of household exposure to hazardous products and cultural factors underlying that exposure.

Results indicate that current Poison Control Center outreach efforts should be expanded. No mother interviewed in the present study had a Poison Control Center telephone number available. This finding was consistent with the results of another study indicating that parents schooled in Mexico were significantly less likely to have called a Poison Control Center before going to an emergency room for pediatric poisoning than were parents schooled in the United States.[18] Poison Control Center outreach messages should be adapted for use in the Spanish-language media, an important source of information for the many Latinos who are not fluent in English.

The messages should address the dangers posed by shared housing and by common products that lack child-resistant packaging, such as rubbing alcohol and medicines from Mexico. Particular attention should be paid to advocating better storage practices, including the use of sturdy cabinet latches and inexpensive but lockable containers, such as small plastic toolboxes. Evidence from the present study indicates that most cabinet latches are not sturdy enough to stand up to assaults by children over time, and that mothers' reports that they have such latches need to be followed up with queries as to whether the latches are still functional.

Clinicians are in a unique position to help prevent poisonings by informing patients about safe storage and use of medicines and household chemicals. For those who do not know English, it is clearly essential to label medications and give instructions in Spanish. Spanish-language handouts on poisoning prevention are available from the American Academy of Pediatrics and regional Poison Control Centers. Above all, clinicians should keep in mind that poverty, crowding, and the inability to read English can have far-reaching effects on children's exposure to toxic substances.

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COMMENTARY

How to do ethnographic research

One of the most important contributions of anthropology is our research methodology, known in the field as "participant observation" but also referred to as ethnography. We believe that people must be understood in context. Cultures are seen as holistic, with each aspect influencing and being influenced by every other. It is not enough to take people's words for things, as is necessary in questionnaires and interviews, because people are notoriously unreliable. Their respect for your authority may lead them to tell you exactly what they think you want to hear. Or they may have other agendas influencing their responses, such as fear of the immigration service. In any case, anthropologists long ago learned that to increase your chances of acquiring valid data (in the statistical sense), you need to make observations a part of the data collection process. With respect to the study of poisoning exposure among children of Mexican-born mothers, it is imperative to study the situation in the homes in areas where children are being poisoned at greater rates than in other areas.

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The authors use the term "ethnography" to describe their methodology. They cite an important article by William Ventres and Richard Frankel entitled "Ethnography: a stepwise approach for primary care researchers."[1] Much of this commentary is based on that article.

Ventres and Frankel define ethnography as "the research process of learning from people about their culture." Traditionally, anthropologists wrote ethnographies—complete descriptions of a culture, including its values, beliefs, marriage patterns, social structure, political system, and so forth—after living 1 to 2 years with the people, observing and participating in their lives. This does not guarantee objectivity, however, because each researcher will be influenced by his or her own biases and preconceptions, and the people will respond to the researchers as individuals, some of whom they will like more than others. It does, however, insure a deeper degree of understanding than can be gained by most field methodologies. An important goal of ethnographic research is to try to get the *emic* perspective—the "natives" views of their own behavior—in addition to the *etic*, or "outsiders," views. For example, many years ago a study was done on high rates of communicable disease in a rural Peruvian town high in the Andes.[2] The problem appeared easily ameliorated by having the people boil water. It was not until researchers went in to study the people that they learned why this was nearly impossible, at least from the people's point of view. For one thing, they believed that "cooked" water was related to illness, and they did not want to compromise their health by boiling the water. For another, during much of the year, fuel for fire was scarce, and collecting it would take time out of an already busy day. Most hearths were too small to fit more than two cooking vessels at a time; space was needed for food. Thus the number of times water could be boiled, using a limited fuel resource and cooking space, was greatly restricted. By learning something about these people, their beliefs, and their lifestyle, researchers came to understand why they were reluctant to boil their water.

Ethnography is defined as a "set of qualitative research methods"[1] that can be used to investigate the human dimensions of health, illness, and disease. It is defined by 3 principles: 1) it is an observational method designed to get at the meanings underlying peoples' behaviors; 2) it focuses on everyday life as events unfold naturally; and 3) its goal is to understand behavior from the point of view of those who are being studied.

Ethnography can be used in conjunction with quantitative studies; prior to quantitative studies, if little is known about which variables to study; or after quantitative studies, to help explain findings in depth. It can also be used independently from such studies when the goal is to understand aspects of medical care related to cultural rules and expectations. Ethnography can help provide insight into seemingly puzzling or contradictory behavior.

Ethnographic research is characterized by 3 fundamental tasks: 1) observing people's behavior; 2) studying what people *say* they do, believe, and think; and 3) interpreting what people *actually* believe and think. There are 5 basic steps to accomplishing these tasks using an ethnographic research plan.

Defining a research question

The research question should convey a rather general theme rather than a specific hypothesis. An important part of this step is for the researchers to examine their own biases and see how they might influence the data collection. These biases must be revealed to the readers when the research is written up. In other words, the researchers must acknowledge their own subjectivity.

Interviewing informants

Open-ended, face-to-face interviews are conducted. The interviewer is on an equal footing with the interviewee, a departure from the standard physician-patient relationship. The researcher must be the curious person who wants to know more about the interviewee's perspective on his or her life experience and beliefs.

Participant observation

The researcher must spend a great deal of time with the informants, interacting socially while discreetly taking systematic notes. In this way, he or she can learn the cultural rules of behavior.

Analyzing observations

Ventres and Frankel describe 3 common principles of ethnographic data analysis: 1) triangulation, or using data from a variety of sources, including interviews, participant observation, and personal diaries; 2) thick description, which involves getting "under the skin" of the people being studied, so that you can see things from their points of view; and 3) saturation, meaning that analysis is seen as completed when no new data or ideas come up.

Reporting results

The authors emphasize the importance of clearly describing your research methodology, revealing any sources of bias, and condensing large amounts of descriptive data.

In order to judge the quality of ethnographic work, Ventres and Frankel suggest that authors and readers ask the following questions: What was the design? Is the text credible? Does the study make sense clinically?

References

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Research Digest

Evidence inconclusive on best treatment for patients who self-inflict harm

Question
Which psychosocial or pharmacological treatments are most effective in patients who have deliberately harmed themselves?

Data sources
Studies were identified by searching MEDLINE, PsycLIT, EMBASE/Excerpta Medica, and the Cochrane Controlled Trials Register; hand-searching 10 journals; reviewing reference lists of identified articles; and contacting experts.

Study selection
Studies were selected if they were randomized controlled trials comparing psychosocial or psychopharmacological treatments with standard or less intensive types of aftercare for patients who engaged in any type of deliberately initiated self-poisoning or self-injury shortly before entering a study.

Data extraction
Data were extracted on characteristics of the patients, type and details of the intervention, and proportion of patients who repeated suicidal behavior.

Main results
Twenty studies with outcome data involving 2452 patients were included. No difference in the repetition of deliberate self-harm existed when the use of problem-solving therapy (4 studies), intensive intervention plus outreach (6 studies), or emergency contact card interventions (2 studies) were compared with standard aftercare; when inpatient behavioral therapy was compared with inpatient insight-oriented therapy (1 study); when general hospital admission was compared with discharge (1 study); when antidepressants were compared with placebo (2 studies); or when long-term therapy was compared with short-term therapy (1 study).

A reduced rate of repetition of deliberate self-harm was found in the experimental groups when dialectical behavior therapy was compared with standard aftercare (subgroup analysis from 1 study: 26% vs 60%, P=0.03*) and when flupenthixol was compared with placebo (1 small study: 21% vs 75%, P=0.003*). A higher rate of subsequent deliberate self-harm was found in patients allocated to the same therapist compared with those allocated to a different therapist (1 study: 18% vs 5%, P=0.02*), but this finding was probably the result of an unequal distribution of patients at risk in the 2 groups. (*P value calculated from data in article.)

Conclusion
There is insufficient evidence to make recommendations on which treatments are the most effective for patients who have recently engaged in deliberate self-harm.

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E. Arensman,
E. Townsend, et al.

Cochrane Review, 12 May 1998. In: Cochrane Library. Oxford: Update Software.

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COMMENTARY

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This review by Hawton et al. summarizes the evidence for psychosocial or pharmacological treatment of individuals after episodes of deliberate self-harm. Suicide attempts or deliberate self-harm are a frequent cause of contact with mental health services. Although people attempting suicide are encountered frequently, no best practices have been established.

Other reviewers have approached this evidence using different definitions and conceptual models. In a study by Rudd et al. that used broader inclusion criteria,[1] our own review of psychosocial interventions[2] was included, but it was excluded by Hawton et al. because the sample included individuals with suicidal ideation without attempts. Hawton et al.'s groupings of studies seem to be less conceptually based than those used by Van der Sande et al.[3] Their review and meta-analysis grouped together interventions that used a cognitive behavioral rationale and reported a summary relative risk ratio for these studies that was statistically significant. Other work has been published since the review by Hawton et al. A recent trial showed that for individuals with fewer than 5 previous attempts, a statistically significant reduction in recurrent suicide attempts occurred in the paroxetine arm compared with the placebo arm.[4]

We have cautioned that although statistical significance has been difficult to show, several trials have reported reductions, which may have clinical significance. The literature clearly indicates that assertive follow-up of individuals who have recently harmed themselves is warranted in the post-discharge period.

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Authors' response:

Dr. Links indicates that our grouping of studies was "less conceptually based than that used by Van der Sande et al." He particularly highlights the category of cognitive behavioral treatment, in which these authors included dialectical behavior therapy (DBT). It is inappropriate to include Linehan's study of DBT with studies of brief (up to 10 sessions) problem-solving therapy, as the former was a 1-year intensive program of individual and group therapy.

Thioridazine for elderly patients with dementia

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Cochrane Review, 14 Aug 1998. In: Cochrane Library. Oxford: Update Software.

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Question

Is thioridazine effective and safe, and does it improve cognitive outcomes in elderly patients with dementia?

Data sources

Studies were identified by searching MEDLINE, EMBASE/Excerpta Medica, PsycLIT, CINAHL, and the Cochrane Group Register of Clinical Trials using the terms thioridazine, Melleril, dementia, and old age, and by reviewing additional published and unpublished studies.

Study selection

Studies were selected if they were randomized trials of thioridazine (used for ≥1 dose) compared with placebo, no treatment, an alternative drug, or behavioral intervention in patients with a degenerative dementia. Studies were excluded from the analysis if treatment allocation was not concealed.

Data extraction

Data were extracted on patient characteristics, allocation procedure, study quality, blinding, interventions used, dropouts, methods of analysis, drug safety, institutionalization, death, and pre- and post-treatment dementia assessment scores. Dementia was assessed using behavioral, clinical global impression, functional performance, and cognitive scales.

Main results

Fifty-one studies were identified. Ten studies met the inclusion criteria; 7 studies had sufficient data for inclusion in the analysis. These 7 studies (published between 1973 and 1992) were double-blind; ranged from 3 to 8 weeks in duration; included between 30 and 610 patients with mean ages between 73 and 80 years; used thioridazine doses of between 10 mg and 200 mg; and included comparisons of thioridazine with placebo, diazepam, loxapine, zuclopenthixol, etoperidone, and chlormethiazole. In 1 study, more patients who received thioridazine than those who received placebo had improvements in anxiety scores, based on an assessment of anxious mood, tension, fear, and insomnia (79% vs 41%, P<0.001*) and agitation, intellect, depressed mood, and behavior at interview (74% vs 42%, P<0.001*); no difference existed for clinical global change or adverse effects.

In 1 study, more patients who received thioridazine than those who received diazepam had improvements in anxiety scores, based on an assessment of agitation, intellect, depressed mood, and behavior at interview (77% vs 65%, P=0.03*); no difference existed for clinical global change or adverse effects. In 1 study, fewer patients who received thioridazine than those who received chlormethiazole had improved behavioral rating scores for items of confusion and alertness (20% vs 47%, P=0.03*), continence (10% vs 37%, P=0.01*), and nocturnal awakening (47% vs 80%, P=0.007*); and patients who received thioridazine had increased dizziness (23% vs 3%, P=0.02*). Thioridazine was not more effective than etoperidone, loxapine, or zuclopenthixol. (*P value calculated from data in article.)

Conclusion

Thioridazine is not more effective than placebo or other neuroleptic drugs for improving the behavioral, global clinical, or cognitive states of elderly patients with dementia. Thioridazine reduced anxiety only when compared with placebo or diazepam and led to worsened behavioral scores and increased dizziness when compared with chlormethiazole.

COMMENTARY

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The treatment of behavioral abnormalities in dementia is a perennial quandary for neuropsychiatrists. Treatment strategies for these problems are largely governed by testimonial data, because few controlled trials exist to guide the way. This is understandable: controlled studies are difficult to do in light of diagnostic heterogeneity, concomitant medical illnesses, and informed consent issues. Furthermore, there are probably many different neurobiological reasons why patients with dementia would develop agitation, aggression, and disruptive behavior.

Although there is widespread use of thioridazine for agitation in dementia, the meta-analysis by Kirchner et al. would suggest cautious use of this compound in the future. The use of this meta-analysis as a basis for conclusions, however, is problematic, because it draws from studies with a diverse mixture of treatment comparisons, diagnostic groups, and rating scales. Surprisingly, thioridazine is superior to placebo or diazepam only on some items from the Hamilton Anxiety Scale but not on global measures of clinical improvement, indicating perhaps that patients' internal experiences and behavior with examiners improve more than global measures of their behavior in groups.

Obviously, one cannot conclude that thioridazine is a superior anxiolytic when compared with diazepam, unless one controls for the level of sedation induced by the 2 drugs. It appears that several non-sedating neuroleptics are as effective in reducing agitation as thioridazine, which would suggest that the sedating properties of thioridazine and related drugs are not as important as was once believed in reducing anxiety and agitation. The important question inevitably becomes whether the risk of extrapyramidal side effects with non-sedating neuroleptics is greater than the risk of cardiovascular and other side effects with drugs such as thioridazine. This question cannot be answered reliably from study data and must still be decided on a case-by-case basis by informed clinicians.

Allele predicted accelerated rate of cognitive decline in Alzheimer's disease

Question

In patients newly diagnosed with Alzheimer's disease, what effect do different apolipoprotein E (Apo E) genotypes have on the rate of cognitive decline?

Design

Inception cohort followed 1–6 years ($\bar{x}$ 2.47 years)

Setting

Health maintenance organization in Seattle, WA

Participants

A total of 201 patients were included. They had all been diagnosed with Alzheimer's disease within the previous year, based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised, and the National Institute of Neurological and Cognitive Disorders and Stroke-Alzheimer's Disease and Related Disorders Association. Patients with other central nervous system conditions or major psychiatric disorders were excluded.

Assessment of prognostic factors

Patients were grouped according to their Apo E genotype: ε2/3 (n=14), ε3/3 (n=75), ε3/4 (n=82), and ε4/4 (n=30).

Main outcome measure

Annual rate of cognitive decline assessed by total scores on the Dementia Rating Scale (DRS) derived from 5 subscales: attention, memory, initiation and perseveration, conceptualization, and construction.

Main results

All patients had baseline and ≥1 DRS total score. At the mean DRS score of 105 for this patient sample, the ε4/4 group had a greater rate of decline than the ε2/3 group (P<0.003). The differences in rate of decline were less pronounced compared with the ε3/3 group (P<0.076) and the ε3/4 group (P<0.055). At a DRS score of 80, the rate of decline in the ε4/4 group was greater than in the ε2/3 group (P<0.001) and the ε3/4 group (P<0.021), with a smaller difference compared with the ε3/3 group (P<0.174) (see Table 1). At both cut-off points, the rate of decline was slower in the ε2/3 group than in the ε3/3 and ε3/4 groups. In addition, older age predicted a slower rate of decline (P<0.001).

Conclusions

Patients newly diagnosed with Alzheimer's disease who were homozygous for the apolipoprotein E ε4 allele had an increased rate of cognitive decline compared with other genotypes. Patients with the ε2/3 allele had a slower rate of decline.

Table 1 *Rate of decline compared with Dementia Rating Scale score*

Score on Dementia Rating Scale	Rate of decline (points/year)			
	ε2/3	ε3/3	ε3/4	ε4/4
105	5.8	9.3	9.6	11.9
80	9.7	18.2	15.8	22.2

S. Craft, L. Teri, S.D. Edland, et al. Neurology 1998;51:149-53.

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COMMENTARY

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The search for biological markers to confirm the clinical diagnosis of Alzheimer's disease (AD) has been prompted by the assumption that new treatments are most likely to slow or halt disease progression rather than reverse existing damage. Human Apo E, previously known for its role in cholesterol transport and plasma lipoprotein metabolism, has emerged as a major genetic risk factor for AD.

The Apo E ε4 allele has been shown to confer an increased risk of AD, occurring in up to 50% of cases.[1] From a clinicopathological viewpoint, the Apo E ε4 allele appears to lower the age of onset of AD and increase the amount of A β deposition in the brain.[2] Few studies support the implications of genotype differences in disease severity or rate of decline.[3, 4] In that context, this study contributes to knowledge about the molecular genetics of AD.

The study includes the largest inception cohort of patients with AD in whom longitudinal data and Apo E status have been reported. Another strength of the study is the use of the DRS's broad range of scores to measure decline and avoid the floor effects of other instruments (for example, the Mini Mental State Examination). Furthermore, the study was able to examine the effects of Apo E genotype status on disease progression. Statistically significant differences were detected in the rate of decline between the ε4/4 group (fastest) and the ε2/3 group (slowest), while similar (intermediate) rates were detected for the ε3/4 and ε3/3 groups. Finally, the results were robust to the manipulation of age at onset as a covariate or as a correlate of rate of decline.

The study provides further evidence for the hypothesis that Apo E plays a mechanistic part in the neuropathological progression of Alzheimer's disease as well as in its onset. The findings support the previously established clinical utility of Apo E testing[5] and suggest its possible role as a prognostic indicator in some patients presenting with dementia.

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Cocaine abuse and dependence linked to genetic risk factors among female twins

K.S. Kendler,
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Br J Psychiatry
1998;173:345-350.

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Question

How much influence do genetic and environmental risk factors have on lifetime cocaine use, abuse, and dependence in women?

Design

A population-based cohort study using data from a twin registry

Setting

Virginia

Participants

A total of 1937 out of 2288 eligible white women (mean age 37 years) were interviewed. Participants were members of female-female pairs listed in the Virginia Twin Registry. Data for 1934 women were included in the analysis; both twins were included for 485 monozygotic (MZ) pairs and 335 (DZ) dizygotic pairs.

Assessment of risk factors

Zygosity was determined blindly by standard questions, photographs, and DNA when necessary. Telephone interviewers, who were blind to information about the co-twin, asked questions about childhood (how often the twins shared the same room at home, were in the same class at school, and were dressed alike); adolescence (how often they had the same friends, were in the same social group, and went out together to films and dances); and adulthood (how much contact they had had in the previous year). These data were used to assess the similarity of environments for each pair of twins.

Main outcome measures

Lifetime cocaine use, abuse, and dependence were assessed by an adapted Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised (DSM-III-R), patient version interview. Cocaine abuse and dependence were diagnosed by using DSM-IV criteria.

Main results

MZ and DZ twins whose co-twins had used cocaine were more likely to use cocaine than those whose co-twins had not used cocaine (odds ratio [OR] 14.2, 95% confidence interval [CI] 8.7 to 23.2 for MZ twins; OR 6.7, 95% CI 3.9 to 11.7 for DZ twins). MZ twins were also more likely to abuse or be dependent on cocaine if their co-twins had abused or been dependent on cocaine (OR 40.8, 95% CI 16.3 to 102.4 for abuse; OR 27.6, 95% CI 9.4 to 81.5 for dependence). For DZ twins, cocaine abuse and dependence did not have statistically significant associations with cocaine abuse (OR 2.70, 95% CI 0.6 to 13.1) or dependence in the co-twin (OR not estimated because no DZ twins were concordant). Tetrachoric correlations were high for cocaine use, abuse, and dependence in MZ twins ($r = 0.73$, $r = 0.80$, and $r = 0.68$, respectively). In DZ twins, the correlation was greater for cocaine use ($r = 0.54$) than for cocaine abuse ($r = 0.18$) or dependence ($r = 0.08$). Models developed to fit data showed cocaine abuse and dependence were influenced mainly by genetic risk factors, which explained 79% of the variance for abuse and 65% of the variance for dependence. For cocaine use, 39% of the variance was explained by genetic and 35% by environmental risk factors.

Conclusion

Lifetime cocaine abuse and dependence in women were mainly influenced by genetic risk factors. Lifetime cocaine use in women was influenced partly by genetic and partly by environmental risk factors.

COMMENTARY

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Family, twin, and adoption studies are the cornerstone of genetic epidemiology. In psychiatry, these paradigms enhance our understanding of putative causal mechanisms, although direct evidence for genetic and environmental determinants remains to be elucidated for the major psychiatric disorders. Many practitioners are optimistic about the recent advances in molecular biology, and they believe that the identification of genetic factors is within our reach for some of these disorders. Evidence from family, twin, and adoption studies provides essential stepping stones for the identification of genetic factors that can be investigated further in linkage and segregation studies.

A combination of these approaches has uncovered compelling evidence for the role of genetic factors in substance abuse (as reviewed in the study by Kendler and Prescott). This study adds an additional piece to this complex puzzle and is a major contribution to the literature because it is the first reported twin study of cocaine use and abuse in women.

The strengths of this study lie in its excellent methodology, including the community-based twin sample, which enhances the generalizability of the findings; the blinding of the interviewers; the use of standardized diagnostic criteria; the examination of multiple sources of potential bias that might attenuate or diminish effect sizes; and the statistical approach used to show twin resemblance for liability to cocaine use and abuse.

The inherent weakness of this study, as reported by the authors, is the small number of twins who had abuse or dependence problems. Although the proportions of cocaine use, abuse, and dependence are similar to what is reported in the National Comorbidity Survey, the small number of affected twins makes it difficult to estimate the magnitude of the genetic effect. It is clear that these findings need to be replicated in a larger sample of female twins. It would be of additional clinical interest to conduct a longitudinal study to determine whether the course and outcome differ in men and women.

The clinical implications of these findings for practice are subtle yet important. They include the need to establish a family history of substance use and abuse and the need to gather information during clinical interviews to distinguish between the use and abuse of substances. These 2 sources of information may be particularly important if future studies show that the magnitude of the genetic effect is associated with differential responses to treatment.

Best Practice

BETWEEN THE LINES

Dietary management of type 2 diabetes mellitus

Mrs. Matthews was a 45-year-old obese nonsmoker with recent-onset type 2 diabetes. She referred herself to Dr. Drysdale because of dissatisfaction with control of her blood glucose, despite taking 10 mg of glyburide per day. Her glucose monitoring record showed fasting values consistently around 100 mg/dL but postprandial values that fluctuated markedly from 80 to 400 mg/dL. Upon additional questioning, she noted that the highest glucose values were related to large meals or binges of sweets following periods of restraint. She also reported that she had lost 20 pounds on 2 occasions by aggressive dieting but had immediately gained the weight back both times. Dr. Drysdale took note of the American Diabetic Association's recent nutritional guidelines[1] and considered these basic questions in his initial approach to dietary management of Mrs. Matthews' hyperglycemia.

How effective is weight loss in controlling blood glucose levels?

Of all dietary modifications, weight loss is perhaps the best documented intervention; a number of trials have shown that hypocaloric diets substantially reduce blood glucose. It is not clear, however, whether glucose improvement is related to weight loss per se or simply to the temporarily decreased caloric intake that takes place during the period of weight loss.

For example, when 30 diabetic subjects were fed a very low-calorie diet, 330 calories per day, for 40 days, the average glucose level decreased from 297 to 158 mg/dL.[2] Although 87% of this reduction occurred by day 10 of the diet, most of the weight loss took place in the subsequent 30 days. When subjects resumed isocaloric feedings, about half of the original glucose gain disappeared even though their original weight loss was preserved.

In a randomized trial comparing 2 diets in diabetic patients, subjects who lost an average of 24 pounds on a 400-calorie diet reduced their fasting blood glucose (FBG) by 104 mg/dL while those who lost the same amount of weight on a 1000-calorie diet reduced their FBG by 61 mg/dL.[3] When the first group switched to the 1000-calorie diet, their FBG climbed to match the second group, despite their losing an additional 15 pounds.

In a study of long-term effects of weight loss in 110 diabetic patients, the 6 subjects who maintained a 30-pound weight loss at 1 year experienced a decline in FBG from 186 to 109 mg/dL. The 20 subjects who lost 15 to 30 pounds had a decline from 191 to 162. The remaining 84 subjects (76%) experienced no discernible improvement in their FBG.[4] This study illustrates the main drawback to weight loss as a tool for glycemic control: most patients are simply unable to achieve and maintain their target body weight. Weight loss is, however, an effective strategy for glucose control for the few patients who are able to achieve it.

What are the benefits of spreading intake throughout the day?

One of the earliest known dietary principles is the advantage of frequent small feedings rather than several large meals. This common sense axiom is based on the principle that type 2 diabetics may retain an adequate insulin response to a modest carbohydrate load but are unable to cope with intakes above a certain threshold.

In a comparison of 2 versus 6 meals per day, the more frequent feedings reduced the daily amplitude of glucose swings (between highest and lowest) from 110 to 59 mg/dL and decreased the peak glucose by about 40 mg/dL but did not affect average glucose levels, because glucose lows were also attenuated.[5]

In a more extreme comparison, patients who took 17 hourly snacks per day experienced a 28% reduction in insulin levels but only a 4% reduction in average blood glucose, compared with subjects taking 3 meals per day.[6] In a recent small crossover trial, an isocaloric 12-snack-per-day diet decreased the average daily blood glucose from 200 to 173 mg/dL, in comparison to a 3-meal-per-day diet. The mean insulin level also decreased by 9.2%.[7]

The chief advantage of this practice, then, is to moderate blood glucose extremes and to reduce insulin secretion. Theoretical drawbacks to frequent feedings include the potential for weight gain and difficulty with compliance. The principle of frequent small feedings has never been tested in a large randomized trial to assess effectiveness and social acceptability. Spreading intake throughout the day with small meals and snacks dampens blood glucose extremes but has only modest effects on average glucose levels.

What is the proper intake of simple sugars and complex carbohydrates?

Traditional teaching in diabetic diets has favored starches over sweets. A considerable body of evidence has essentially contradicted this maxim, and there are currently no clear answers as to the appropriate composition of carbohydrates in a diabetic diet.

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Between the Lines is a case-based review of commonly asked clinical questions. Responses to the questions will examine the "fine print" of the evidence in order to bring primary data about diagnostic and clinical efficacy directly to the reader. The objective in presenting this quantitative information is to encourage and empower clinicians to weigh risks and benefits in tailoring their clinical decisions to the needs of their individual patients.

Readers are invited to submit Between the Lines articles to be considered for publication by WJM to Nate Link, MD, c/o WJM, PO Box 7690, San Francisco, CA 94120-7690.

A prominent tool in this area of research has been the glycemic index, a standardized measure of blood glucose response to the ingestion of given substances. Lists of the glycemic index (GI) for most common foods have been reported in the literature and yield a number of surprises. For example, using white bread as a standard GI of 100, an equivalent carbohydrate content of honey yields a GI of 126; of sucrose, 86; of bananas, 79; of frozen peas, 74; and of ice cream, 52.[8]

These data are complicated, however, by the observation that when foods are ingested in mixed meals, the effects of fat and fiber on gastric emptying and intestinal absorption may produce unpredictable results. To test this effect, glycemic responses to 3 common foods (bread, rice, and spaghetti, with GIs of 100, 79, and 61 respectively) were tested in each of 12 diabetic subjects as 50-gram portions in otherwise identical mixed meals. The measured values were similar to the predicted effects (bread 100, rice 75, and spaghetti 54), with consistent responses among different subjects.[9] In another study, however, differences in the GI index overpredicted differences in glycemic responses to mixed meals.[10] The authors of the latter study have strongly cautioned the medical community against a wholesale adoption of the GI in dietary planning.[11]

A more recent trial pitted a traditional (high carbohydrate) diabetic diet against an isocaloric experimental diet that emphasized sucrose- and fructose-rich carbohydrates rather than usual starches such as bread and potatoes. The incremental glucose response to the experimental diet was only 3% that of the traditional diabetic diet.[12]

The chief dietary contributors to hyperglycemia are carbohydrates of all types. In general, sweets may be substituted for complex carbohydrates without harming glucose control. The glycemic index may become a useful tool for meal planning.

What is the appropriate lipid composition in a diabetic diet?

On first glance, a high-fat diet would appear to be the perfect solution to glucose intolerance. The risk of coronary artery disease, however, has led the ADA in the past to recommend strict controls in dietary fat intake and to emphasize carbohydrates as the chief energy source. Nonetheless, as recent data challenge blanket assumptions about the role of diet in lipid management, other approaches are gaining acceptance.

Of specific interest is the relationship between coronary risk and the types of fats that are consumed. For example, compared with a traditional high-carbohydrate diet, a high-monounsaturated fat diet (50% fat) decreased blood glucose by 14%, serum triglycerides by 25%, and insulin doses by 14%, without affecting LDL cholesterol or weight in type 2 diabetics on insulin therapy.[13]

In a follow-up study of 42 diabetics on glipizide therapy, the high-carbohydrate diet increased glucose, triglyceride, and insulin levels by 12%, 9%, and 10%, respectively, compared with the high monounsaturated fat diet.[14] Body weight and low- and high-density lipoprotein levels were unaffected. The long-term effects of the high monounsaturated fat diet have not been assessed by a large-scale randomized trial under "real-life" conditions. Regardless of total fat intake, diabetic diets should emphasize monounsaturated fats over other dietary sources of fat. Replacement of carbohydrates by monounsaturated fats may be considered in refractory cases, but weight and lipid profile should be closely monitored.

Taking notice of Mrs. Matthews' failure to sustain weight loss in the past and her acceptable fasting blood glucose, Dr. Drysdale focused on fluctuations in her postprandial values as they related to carbohydrate intake. He advised her to reduce the size and increase the time between meals, to eat small snacks, and to add sweets to her daily carbohydrate quota to avoid periodic cravings. He emphasized the value of monounsaturated fats but decided not to press for an increase in total daily fat intake. He referred Mrs. Matthews to a dietician for intensive instruction to integrate these principles into a modestly hypocaloric diet.

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TOPIC IN REVIEW

Hormone replacement therapy: where are we now?

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The number of postmenopausal women is increasing worldwide. Hormone replacement therapy is the standard first-line treatment of menopausal symptoms, but uncertainty about important long-term risks (such as breast cancer) and benefits (such as the prevention of coronary heart disease) remains. Every week new papers are published, some contradicting previous reports, yet recommendations must be made before definitive answers are available. This paper reviews recent studies of the risks and benefits of hormone replacement therapy.

This review is based on a computer search of the 1990 to 1999 literature on MEDLINE using the following key words: estrogen, hormone replacement therapy, menopause, and women's health. Only recent papers are cited.

SYMPTOM RELIEF

Vasomotor symptoms

For many women, the onset of vasomotor symptoms marks the onset of the menopause transition. Estrogen replacement remains the gold standard for relief of hot flashes. In the Postmenopausal Estrogen/Progestin Intervention trial, there was no additional benefit of estrogen-progestin combinations over estrogen alone in reducing vasomotor symptoms.[1]

Menopausal symptoms may be useful for identifying premenopausal women at higher risk for low bone mineral density and, perhaps, osteoporosis. In the Women's Healthy Lifestyle Project, bone mineral density at the spine and hip was significantly lower in women with hot flashes and menstrual cycle irregularities than in asymptomatic women.[2]

Vaginal dryness and urinary symptoms

Vaginal dryness and urinary symptoms may begin in the perimenopause or later. Topical estrogen is as effective as systemic therapy. In addition to vaginal creams, which may increase serum concentrations of estrogen, local estrogen therapy is now available in multiple preparations, including a silastic vaginal ring requiring replacement every 3 months.[3]

In a randomized clinical trial, urinary tract infections were reduced by the use of vaginal estrogen.[4] The effect of hormone replacement therapy on urinary incontinence has been inconsistent.[5,6]

COGNITION AND DEPRESSIVE SYMPTOMS

Perimenopausal and postmenopausal women often complain of "fuzzy thinking," trouble concentrating, or memory loss. In a randomized clinical trial, Sherwin found that "add-back" estrogen therapy in premenopausal women rendered estrogen-deficient (by gonadotropin-releasing hormone agonist treatment) specifically enhanced verbal memory but did not enhance visual memory.[7] Anxiety, cognitive symptoms, and affective symptoms did not differ by treatment assignment in the Postmenopausal Estrogen/Progestin Interventions Trial trial, but women with severe symptoms were not included.[1]

In a recent meta-analysis of 26 studies of hormone replacement therapy and depressed mood, Zweifel and O'Brien found that women using hormone replacement therapy had less depressed mood than women not using estrogen, that estrogen alone reduced depressed mood more than the combination of estrogen with progesterone, and that androgen replacement was associated with the greatest benefit.[8]

DISEASE PREVENTION

Osteoporosis prevention

Estrogen is the treatment of choice to prevent postmenopausal osteoporosis, and prevention of osteoporosis-related fractures currently constitutes the strongest indication for long-term estrogen use.[9] In observational studies, hormone replacement therapy reduces hip fracture by 30% and vertebral fracture by 50%. Two small clinical trials showed a significantly reduced number of vertebral fractures in estrogen users, but there was no difference in clinical fractures after 4.1 years in the Heart and Estrogen/Progestin Replacement Study, a random-

Summary Points

- As the standard first-line treatment of menopausal symptoms, estrogen improves vasomotor symptoms, vaginal dryness, and recurrent urinary tract infections.
- Estrogen should be initiated at the time of menopause and taken indefinitely for osteoporosis prevention and treatment; alternatively, benefit can still be achieved if hormone replacement therapy is not started until age 60 or later.
- Endometrial cancer risk is increased in estrogen users unless concurrent progestin therapy is added, either cyclically or continuously.
- Uncertainty remains about the important long-term risk of breast cancer, shown in observational studies to have increased by 32% after 5 years of hormone replacement therapy.
- The risk of venous thromboembolic events is increased by two- to three-fold.
- Surrogate markers for cardiovascular protection are improved by estrogen, although the use of hormones solely for prevention of coronary heart disease should not be recommended until clinical benefit has been demonstrated in randomized trials.

ized clinical trial of hormone replacement therapy versus placebo in nearly 3000 postmenopausal women.[10]

Though estrogen reduces bone loss at the hip and spine in postmenopausal women of all ages, timing of hormone replacement therapy may be important. In the Rancho Bernardo Study, women who had taken estrogen for only 5 to 10 years immediately after menopause had no discernable benefit by age 75, while bone density was nearly as good in women who initiated therapy after age 60 as in women who had used estrogen continuously since menopause.[11] Accordingly, the National Osteoporosis Foundation has recently recommended starting replacement therapy after age 60.

An estrogen dose equivalent to 0.625 mg of conjugated equine estrogen has been the standard for the prevention of bone loss, but recent studies suggest that a lower dose (0.3 mg) of esterified estrogen[12], 0.5 mg of micronized estradiol[13], or 0.3 mg of conjugated equine estrogens is adequate to prevent bone loss in most women. The addition of androgens to the standard regimen of hormone replacement therapy may increase bone formation; combination therapy with the most commonly used progestins provides no added benefit to estrogen alone.[14]

Calcium supplementation potentiates the effect of estrogen on bone.[15] Calcium alone or with vitamin D has been shown in clinical trials to prevent hip fractures in elderly women.

In the past 10 years 3 new modalities—alendronate, raloxifene, and calcitonin—have been approved for prevention or treatment of osteoporosis, or both.

Alendronate has been approved for prevention and treatment of osteoporosis. Results from the Fracture Intervention Trial of 6450 postmenopausal women aged 55 to 81 years showed that treatment with alendronate, 10 mg daily, substantially reduced the risk of vertebral, hip, and wrist fractures in older postmenopausal women who had osteoporotic bone mineral densities[16] or existing vertebral fractures at baseline.[17]

Raloxifene, a selective estrogen receptor modulator, has also been approved for prevention of osteoporosis. In the Multiple Outcomes of Raloxifene Experience study, a randomized clinical trial involving 7705 osteoporotic women, the relative risk of vertebral fractures after 24 months was significantly reduced by 44% in the women treated with 60 mg/day of raloxifene compared to placebo.[18]

Calcitonin has also been approved for treatment of osteoporosis. In the Prevent Recurrence of Osteoporotic Fracture (PROOF) Study, 200 IU/day intranasal salmon calcitonin over 5 years resulted in a 39% decrease in the rate of new and/or worsening vertebral fractures.[19] Calcitonin is usually used for only a few years and is most effective in reducing pain in women with vertebral fractures.

At the present time, estrogen remains the usual first-line preventive or therapeutic agent for women with osteoporosis. Alendronate is chosen for women with severe disease and particularly those most at risk for hip fracture. Raloxifene may prove to be the drug of choice for long-term use in women with or at risk of vertebral fractures because it has fewer side effects and risks than estrogen.

Coronary heart disease prevention

Because coronary heart disease is the commonest cause of death in postmenopausal women, its prevention would be the strongest indication for universal use of hormone replacement therapy. Most of more than 30 observational studies have reported a 30% to 50% reduced risk of coronary heart disease in women using estrogen alone or with progestin.[20] Women who take hormones tend to be educated and affluent, to have more favorable risk factors, and to be unusually compliant—all factors that could spuriously elevate the apparent benefit of estrogen.[20] Therefore, randomized trials that equalize the distribution of both known and unknown determinants of medication use are required to confirm findings in observational studies.

The Postmenopausal Estrogen/Progestin Interventions Trial, a 3-year randomized clinical trial in 874 healthy postmenopausal women, provided 3-year placebo-controlled evidence of improvement in cardiac risk factors. Women assigned to hormone replacement therapy had 12% lower low-density lipoprotein cholesterol and 12% higher high-density lipoprotein cholesterol levels without significant changes in weight, blood pressure, or glucose metabolism.[21] Others have shown that estrogen can induce favorable changes in apolipoproteins, fibrinogen, Lp(a), PAI-1, antithrombin III, homocysteine, endothelial function, vascular reactivity, and blood flow. Studies have also shown estrogen's antioxidant and calcium channel blocking activity.[22]

The first large randomized double-blind clinical trial to question whether changed coronary heart disease risk factors translate into reduced coronary heart disease events was reported recently. The Heart and Estrogen/progestin Replacement Study, a secondary prevention trial, evaluated hormone replacement therapy versus placebo in 2763 women with coronary heart disease at baseline and found no significant difference between the 2 treatment groups after an average of 4.1 years.[10] A significant time trend was reported, however, with a 50% increase in cardiac morbidity and mortality in the first year after randomization to the hormone replacement therapy group and fewer events in the last 2 years. Given these findings, hormone replacement therapy should not be initiated to prevent new events in women with preexisting coronary heart disease. On the other hand, if a woman with coronary heart disease has tolerated hormone replacement therapy for 2 years, then it might be beneficial to continue.

Results from several other clinical trials are expected within the next decade. Meanwhile, all women can benefit from not smoking, regular exercise, and a healthy diet. For women with established coronary heart disease or with high low-density lipoprotein cholesterol or low high-density lipoprotein cholesterol, HMG Co-A reductase inhibitors (statins) have been shown in clinical trials to reduce coronary heart disease events.

Dementia reduction

A meta-analysis of 10 observational studies of postmenopausal estrogen use and risk of dementia[23] suggested a 29% decreased risk, but the findings of the studies were heterogeneous and probably subject to the influence of self-selection because healthier, more educated women tend to choose hormone replacement therapy. Clinical trials of estrogen therapy in women with Alzheimer's disease are too small, too short, and too little controlled to draw any conclusions. In spite of plausible biological mechanisms by which estrogen might reduce the risk for or severity of dementia, randomized placebo-controlled trials, now in progress, are necessary to establish benefit.

Colon cancer risk reduction

Several studies have found that current or recent users of either estrogen or combined hormone replacement therapy had a significantly reduced relative risk of colon cancer.[24] This association is now being studied in ongoing clinical trials.

RISKS OF HORMONE REPLACEMENT THERAPY

Endometrial cancer

All studies show an increased risk of endometrial cancer in women taking unopposed estrogen, although endometrial cancer is rare in women taking combined therapy.[25] In the Postmenopausal Estrogen/Progestin Interventions Trial, unopposed estrogen therapy increased the risk of atypical or complex endometrial hyperplasia, a premalignant lesion, by 10% per year.[21] No such hyperplasia or endometrial cancer was seen in women when cyclic or continuous medroxyprogesterone acetate was added to estrogen. Therefore, combination therapy should be recommended to all women who have not had a hysterectomy. Micronized progesterone, now FDA-approved and available in the United States, was shown in the trial to be equally effective, yet with a better cardiovascular risk profile.[21]

Breast cancer

Breast cancer is the risk most dreaded by women. A 1997 reanalysis of 51 observational studies showed a 32% increased risk of breast cancer among women who had used hormone replacement therapy for 5 years or longer.[26] While this risk has yet to be confirmed in randomized clinical trials, the possibility is sobering and points to the desirability of limiting exposure to hormone replacement therapy to 5 years or less. The selective estrogen receptor modulators like tamoxifen and raloxifene may prevent breast cancer and preserve bone in postmenopausal women.

Other risks

In clinical trials, estrogen therapy has been shown to increase the risk of gall bladder disease by 40% and to increase the risk of venous thromboembolic events two- to three-fold.[10] A recent review[27] of other conditions possibly caused or prevented by hormone therapy showed no consistent association of hormone replacement therapy with osteoarthritis or rheumatoid arthritis, a nearly threefold increased risk of systemic lupus erythematosus, an increased risk of asthma, and an increased risk of Raynaud's syndrome (only with unopposed estrogen). Pancreatitis is seen rarely in women with hypertriglyceridemia.

INDICATIONS FOR HORMONE REPLACEMENT THERAPY

On the basis of current knowledge, the following recommendations seem reasonable:

1. Any woman who has troublesome menopausal symptoms and does not have contraindications to hormone replacement therapy (liver disease, undiagnosed vaginal bleeding, or a history of deep vein thrombosis, pulmonary embolus, or estrogen-dependent cancer) should be offered hormone replacement therapy for symptom relief.
2. If hormone replacement therapy is used for prevention of osteoporosis, it must be continued indefinitely after menopause. In many women, if not most, estrogen can be initiated at age 60 or 65, because most fractures occur after age 65. Reducing the duration of treatment by half would be expected to offer protection at reduced cost and possibly to decrease the risk of any breast cancer associated with hormone replacement therapy.
3. Until clinical trial data showing benefits are available, hormone replacement therapy should not be recommended for prevention of coronary heart disease. Statin therapy is a reasonable alternative.
4. Careful monitoring must accompany the commitment to hormone replacement therapy. Unscheduled bleeding must be investigated to rule out endometrial pathology. Annual mammography for breast cancer surveillance is necessary as well.

CONCLUSIONS

The menopausal transition is important both from the standpoint of symptoms and as a risk factor for bone loss and possibly other chronic diseases. The optimal paradigm for menopausal health will depend upon each indi-

vidual woman's desires, perceived and actual risks, and anticipated benefits.[28] As stated during the Canadian Consensus Conference on Menopause and Osteoporosis, "Recommendations for practice must be based on scientific evidence with ongoing research to determine the most effective interventions."[29] The only clear-cut indications for hormone replacement therapy are to relieve symptoms and prevent or treat vertebral fracture. The most important challenge is to keep abreast of new findings as results of more randomized clinical trials of hormone replacement therapy become available.

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capsule

The pill is safe for women with Crohn's disease Oral contraceptives have little impact on the severity of Crohn's disease, French researchers have found, although many women with the disease are advised to avoid them (Gut 1999;45:218-222). In a study of over 300 women with stable disease, women who used oral contraceptives did not have more flare ups during follow up than the rest. Smoking, on the other hand, emerged as a clear risk factor. Women with Crohn's disease should be allowed the same choice of contraceptives as everyone else, the researchers conclude.

capsule

Kinder colonoscopy for screening Radiologists at the Mayo Clinic are convinced that virtual colonoscopy is the coming technique for screening for colorectal cancer—although they believe more evaluation is needed (Gut 1999;44:301-305). Data obtained using a spiral computed tomographic scanner are processed off-line to produce two- and three-dimensional images. The patient's colon must be distended with gas or air, but the procedure takes only two minutes and the exposure to radiation is about the same as a barium enema. A prospective trial of 70 patients found that for lesions of 0.4 inches or more, the sensitivity was 75% and the specificity was 90%.

MEDICINE CABINET

How to treat allergic rhinitis

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INTRODUCTION

Allergic rhinitis is an IgE-mediated inflammatory disease of the nasal mucosal membranes characterized mainly by sneezing, rhinorrhea, nasal pruritis, and congestion. It is the most common form of rhinitis, affecting 20 to 40 million Americans annually, and it is considered one of the most prevalent chronic diseases in the United States.[1] It is also well documented that allergic rhinitis can negatively impact the quality of life and contribute significantly to loss of work productivity.[2]

Allergic rhinitis may be categorized as seasonal "hay fever" or perennial (when symptoms persist year-round). Often, patients may react to multiple allergens and have seasonal exacerbation of symptoms in addition to perennial rhinitis. Tree, grass, and weed pollens are common seasonal allergens because they become airborne in large concentrations during a particular season of the year. Important perennial allergens include house dust mites, indoor molds, animal dander, and occupational allergens.

MANAGEMENT OVERVIEW

Treatment options for allergic rhinitis include allergen avoidance, use of pharmacological agents for prevention and control of symptoms, and allergen immunotherapy for desensitization of patients in whom avoidance strategies and pharmacotherapy have failed to produce a satisfactory response.

ALLERGEN AVOIDANCE

Whenever possible, environmental control measures should be emphasized as a fundamental part of the treatment plan. For instance, patients with pollen or outdoor mold allergies should remain in closed environments whenever possible. Patients sensitive to dust mites should enclose all mattresses and pillows with allergen-proof casings and eliminate carpeting, if possible, to reduce exposure; bedclothes should be frequently laundered in hot water to remove allergens. Although not always feasible, patients with animal allergies should consider removal of pets from home.

Antihistamines

Antihistamines (H1-antagonists) are typically prescribed as first-line agents for allergic rhinitis. They exert their actions by competitively antagonizing histamine at the H1- receptor sites and thereby suppress symptoms attributable to histamine release, such as sneezing, rhinorrhea, nasal itching, conjunctival itching, and lacrimation. Antihistamines, however, are generally not effective in alleviating nasal congestion.

First-generation antihistamines

Various 1st-generation antihistamines are widely available with and without prescription. Although effective and economical, the usefulness of these agents is limited by their sedative and anticholinergic properties due to penetration of the central nervous system and poor receptor specificity.

All 1st-generation antihistamines are sedating to some degree and may cause performance impairment in 10% to 40% of users.[3,4] In general, the ethanolamines (e.g., diphenhydramine) and phenothiazines (e.g., promethazine) are the most sedating. The ethylenediamines (e.g., pyrilamine) cause moderate sedation, and the alkylamines (e.g., chlorpheniramine, brompheniramine) are considered the least sedating. The use of 1st-generation antihistamines at bedtime, which are less expensive, and newer nonsedating agents during the day has been advocated as a cost-saving strategy. This therapeutic approach may not be cost-effective, however, as residual effects of the bedtime dose may result in daytime sedation and performance impairment.[1,3]

The anticholinergic effects of 1st-generation antihistamines (dry mucous membranes, urinary retention, blurred vision) may preclude their use in certain patients. Elderly patients are especially sensitive to these adverse effects. These older agents should be used cautiously in patients with narrow angle glaucoma or prostatic hypertrophy or in those taking other medications that may potentiate these side effects.

Although 2nd-generation antihistamines are generally prescribed due to ease of dosing and favorable side-effects profile, clinicians should be cognizant of available nonprescription antihistamines, as many patients may be self-managing with over-the-counter products (see Table 1).

Second-generation antihistamines

The newer antihistamines are devoid of anticholinergic and sedative effects with the exception of cetirizine, which

Table 1 *Selected 1st-generation antihistamines*

Generic	Brand	Usual doses
Brompheniramine	Dimetane, others	4 mg q 6-8 hours Extended Release: 12mg q 12 hours
Chlorpheniramine	Chlor-Trimeton, others	4mg q 6-8 hours Extended Release: 12mg q 12 hours
Clemastine	Tavist, others	1.34-2.68mg q 12 hours
Diphenhydramine	Benadryl, others	25-50mg q 6-8 hours

Note: available OTC, often in combination with various decongestants, analgesics, and antitussives

Table 2 *Second-generation antihistamines*

Generic	Brand	Onset	T Ω	Usual doses	Cost per month	Comments
Astemizole *(discontinued June 1999)*	Hismanal	2-5 days	20-24 h (metabolite 10-20 days)	10mg po qd on empty stomach	$68.56	Avoid concomitant use with P450 3A inhibitors & proarrhythmogenic agents
Cetirizine	Zyrtec	Within 1 h	7-9 h	5mg-10mg po qd	$55.80	Also available in syrup (5mg/5ml); may cause drowsiness
Fexofenadine	Allegra	1 h	14-18 h	60mg po bid	$59.30	Active metabolite of terfenadine-devoid of cardiotoxic risk
Fexofenadine/ Pseudoephedrine	Allegra-D			60mg/120mg po bid	$66.71	
Loratadine	Claritin	1 to 3 h	12-15 h	10mg po qd	$65.40	Also available in syrup (5mg/5ml) & rapidly disintegrating tablets
Loratadine/ Pseudoephedrine	Claritin-D 12			5mg/120mg po bid	$73.80	
	Claritin-D 24			10mg/240mg po qd	$72.00	
Azelastine	Astelin	Within 1 h	22-25 h	2 sprays per nostril bid	$53.71	May cause drowsiness

Cost: based on average wholesale prices (AWP), May 1999

may be mildly sedating in some patients. The low incidence of side effects is attributed to their high selectivity for peripheral H_1-receptors and low propensity to cross the blood-brain barrier. Three 2nd-generation antihistamines for oral administration are currently available in the United States: cetirizine, fexofenadine, and loratadine. All appear effective in mitigating the symptoms of allergic rhinitis. Table 2 lists available agents and dosages.

Cardiotoxicity associated with astemizole and terfenadine is the most serious side effect associated with the 2nd-generation antihistamines. Serum accumulation of these agents may deleteriously prolong the QT interval. Serious ventricular arrhythmias (including Torsades de pointes), cardiac arrest, and death have ensued as a result of overdoses and concomitant use of medications that impair the metabolism of terfenadine and astemizole (potent inhibitors of cytochrome P450 3A4 isoenzymes, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, fluoxamine). These reactions and interactions have not been associated with the currently available agents. (Both terfenadine and astemizole have since been voluntarily withdrawn from the US market; terfenadine has been replaced with its nonarrhythmogenic metabolite, fexofenadine.)

Azelastine is a new topically administered 2nd-generation antihistamine that has demonstrated efficacy in improving both early- and late-phase symptoms of allergic rhinitis.[5] Symptomatic response may be seen as early as 30 minutes after dose.[6] In comparative trials, intranasal azelastine appears equally as efficacious as oral antihistamines but generally less effective than corticosteroids in relieving nasal symptoms.[6] The most commonly reported adverse effects are bitter taste, application site irritation, and somnolence. Azelastine is administered 2 sprays per nostril twice daily.

Decongestants

Nasal congestion is a common complication of allergic rhinitis. Congestion resulting from initial allergen exposure is usually limited; generation of other inflammatory mediators (e.g., leukotrienes) contributes, however, to the prominence of congestion in the late-phase inflammatory response period.[7,8] Consequently, many patients will require a decongestant in addition to antihistamine therapy. Decongestants are also useful in clearing nasal passages at the onset of intranasal corticosteroid therapy to improve drug delivery.

Decongestants exert their effects by activation of alpha-adrenergic receptors in the vascular smooth muscle of the respiratory mucosa, thereby causing vasoconstriction in the turbinates. Oral formulations such as pseudoephedrine and phenylpropanolamine are available alone or in combination with various antihistamines. Decongestants may produce unwanted side effects, such as excitation of the central nervous system (e.g., insomnia, restlessness, agitation), tachycardia, urinary retention, and elevations in blood pressure. These agents should be administered cautiously in patients with hypertension, hyperthyroidism, diabetes mellitus, cardiovascular disease, or urinary obstructive diseases.

Topical decongestants (e.g., oxymetazoline, xylometazoline) can rapidly improve symptoms with minimal systemic effects. However, overuse may lead to the development of rhinitis medicamentosa (rebound congestion associated with nasal hyperreactivity, mucosal swelling, and tolerance).[9] For this reason, topical decongestants are contraindicated for chronic nasal congestion, and their use should be limited to 3 to 5 days of therapy.

Corticosteroids

The use of intranasal corticosteroids is increasingly becoming first-line therapy for many patients with allergic rhinitis, especially those with moderate to severe symptoms or those with perennial allergic rhinitis in which nasal symptoms predominate.[10] Intranasal corticosteroids specifically inhibit the allergic inflammatory processes that contribute to the late-phase response of nasal congestion. When used prophylactically, they can also inhibit the early-phase response to allergens.[11] Overall, they are effective in relieving sneezing, nasal itching, rhinorrhea, and congestion.

Table 3 lists available intranasal corticosteroids, along with dosing information and comparative costs. In general, these agents are considered more cost-effective for use as monotherapy than 2nd-generation antihistamines. A recent meta-analysis found intranasal corticosteroids to be more effective than oral antihistamines in reducing nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, and total nasal symptoms.[12] No significant difference was detected for nasal discomfort, nasal resistance, and eye symptoms. No particular product has demonstrated clinical superiority; selection of drug should be based on factors such as response, ease of administration, cost, and formulation.

Application site irritation (e.g., nasal irritation, burning, or sneezing after administration) is the most commonly encountered side effect. Patients complaining of local irritation may be switched to various aqueous formulations. Although rare, mucosal erosion and septal perforations have been reported with long-term use.[13] To minimize septal irritation, patients should be instructed to direct the spray upwards and toward the lateral portion of the nose. Periodic examination of the nasal septum should be performed.[1]

Although systemic effects from intranasal corticosteroids at recommended doses are considered minimal, there are some concerns regarding long-term exposure. Reports of posterior subcapsular cataract formation have been linked with the use of intranasal or inhaled corticosteroids;[14] however, more recent prospective trials did not reveal evidence of posterior subcapsular cataract formation or elevation in intraocular pressure.[15,16]

In 1998, the FDA's advisory committees on pulmonary and allergy drugs and on metabolic endocrine drugs convened to assess data suggesting that intranasal corticosteroids may have an effect on growth velocity in children. Consequently, a new class labeling for pediatric use of inhaled and intranasal corticosteroids was mandated. At this time, the long-term significance of growth velocity reduction on final adult height is unknown. The FDA recommends routine monitoring of growth in pediatric patients using intranasal corticosteroids and titration to the lowest effective dose to minimize systemic risks.

Patient education is essential in ensuring proper use and compliance to intranasal corticosteroid therapy. Patients should be instructed on instillation techniques and informed about the possible delay in symptomatic response. Assessment of maximal response may require a therapeutic trial of several weeks. The drug should be administered regularly on a daily basis, rather than as needed for rescue relief.

For patients with severe disease, the combined use of intranasal corticosteroids and antihistamines may be necessary to control symptoms. The use of oral corticosteroids should be reserved for patients with severe exacerbations or intractable disease due to high risk of systemic adverse effects.

Cromolyn sodium

Cromolyn sodium stabilizes mast cells and thereby prevents the degranulation of chemical mediators upon antigen presentation. Intranasal cromolyn ameliorates symptoms such as sneezing, rhinorrhea, and nasal pruritis but lacks efficacy for nasal congestion. Cromolyn

Table 3 *Intranasal corticosteroids*

Generic	Brand	Usual dose per nostril	Formulation	Inhalations per bottle	Cost per month
Beclomethasone dipropionate	Beconase	1-2 sprays bid	Aerosol	200	$25.85-$51.69
	Beconase AQ	1-2 sprays bid	Aqueous	200	$26.50-$53.00
	Vancenase	1-2 sprays bid	Aerosol	200	$25.56-$51.12
	Vancenase AQ	1-2 sprays bid	Aqueous	200	$34.73-$69.47
	Vancenase DS	1-2 sprays qd	Aqueous	120	$25.30-$50.59
Budesonide	Rhinocort	2 sprays bid or 2-4 sprays qd	Aerosol	200	$21.70-$43.40
Flunisolide	Nasarel	1-2 sprays bid	Aqueous	200	$23.02-$46.03
Fluticasone	Flonase	1-2 sprays qd	Aqueous	120	$24.94-$49.87
Mometasone	Nasonex	1-2 sprays qd	Aqueous	120	$24.96-$49.92
Triamcinolone acetonide	Nasacort	1-2 sprays qd	Aerosol	100	$25.42-$50.83
	Nasacort AQ	1-2 sprays qd	Aqueous	120	$19.39-$38.78

Cost: based on average wholesale prices (AWP), May 1999

is generally less efficacious than intranasal corticosteroids.[17] Therapy adherence may be problematic, as it necessitates frequent dosing (3 to 4 times daily). However, cromolyn may be safely administered, even to very young children, with negligible side effects. Intranasal cromolyn is now available without prescription. Patients should be advised to initiate therapy with cromolyn before the start of the allergy season or in anticipation of allergen exposure.

Ipratropium bromide

Ipratropium bromide is a well-tolerated topical anticholinergic agent that is available in a 0.03% nasal formulation. It is indicated for rhinorrhea associated with allergic and nonallergic perennial rhinitis. (A 0.06% formulation is approved for rhinorrhea associated with the common cold.) This agent quickly and effectively reduces nasal hypersecretion but has no effect on other symptoms of rhinitis such as sneezing and congestion. The most commonly reported adverse effects are nasal dryness and epistaxis.[18] The recommended dose of intranasal ipratropium bromide is 2 sprays per nostril 2 to 3 times daily.

CONCLUSION

Pharmacotherapy remains the mainstay of management in patients with allergic rhinitis. Given the wide selection of available agents, the ideal regimen should be individualized to reflect disease severity and specific symptoms. Factors such as the potential for side effects, risk for drug interactions, ease of administration, and cost should also be considered. Most importantly, patients should be routinely followed to assess therapeutic response and to monitor for side effects or complications.

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ANY QUESTIONS?

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CURBSIDE CONSULT

How credible is the science behind cosmetic skin creams?

In order to answer this question it is important to separate the work done by cosmetic chemists in basic science, product development, and safety testing from the spin put on that work by salespeople, fashion magazine "editorials," and advertising companies promoting the creams, all of which mainly measure success by product sales.

Cosmetic chemists' research is aimed at providing their employers with a competitive edge. Because most of their results are financially sensitive, they are never published. The work that is published often appears in conventional medical journals and is subjected to the same rigorous review process as other articles. In addition, groups such as the International Federation of Societies of Cosmetic Chemists regularly have congresses where scientific papers are presented. The presentations abstracted in the proceedings from the most recent congress, held in Sydney in 1996, are of varying quality; some are at the cutting edge of science whereas others are more dubious.[1]

The benefit of face creams may be mostly in the mind.

Cosmetics are not pharmaceutical agents

It is important to remember that cosmetics, by definition, do not alter the structure or function of the skin, or they would be classed as pharmaceutical agents. There are 2 broad groups of cosmetics: makeup and skin care products. The use of well-applied makeup to add color, accentuate the lips and eyes, conceal blemishes, or relieve dryness or oiliness may enhance a person's physical appearance and sense of well-being.[2]

Cosmetics are luxury items, designed to make the user feel better, irrespective of whether they have any lasting impact on the skin.

On the other hand, skin care products have very little substantive science to commend them. Although extensive comparative research has been done using endpoints such as skin barrier function and epidermal cell turnover to produce products that perform these functions well, the basic assumption that such products are required for skin health and maintenance is questionable.

A basic understanding of skin physiology, skin aging, skin typing, pores, skin allergy, liposomes, collagen and elastin, hormones, and vitamins is required to validate the science reported in skin cream advertisements. Dry skin looks rough; moist skin looks smooth. How rough (dry) or smooth (moist) the skin appears depends on the hydration of the stratum corneum and its thickness. In the ichthyoses (genetic conditions that produce the appearance of dry skin), the skin's moisture content is normal. Thickening of the stratum corneum produces the appearance of dryness.[3] These conditions respond only partially or not at all to moisturizers. Most people do not need moisturizers.

Skin moisturizers act in 2 ways: as an emollient, by providing water to the surface of the skin, and by preventing transepidermal water loss, about 500 ml per day in temperate climates. The second action is more prolonged. The most effective moisturizers are agents such as white soft paraffin that provide a waterproof seal on the skin, allowing it to be hydrated from within. Because white soft paraffin is greasy and difficult to rub into the skin, it is formulated into combinations of water and oil that are more user-friendly, such as 10% glycerine in sorbolene or 5% olive oil in aqueous cream. The oil component contributes most of the moisturizing effect; the water component makes it easier to apply to the skin. More expensive products do not moisturize the skin any more effectively but may have a nicer texture, rub into the skin more easily, and have a superior fragrance.

The effectiveness of skin foods that nourish the skin, vitamins (in particular vitamin E), or hormonal extracts that replenish the skin is not supported by convincing science, and so these products are not recommended. Liposomes are a delivery system that encapsulates a cosmetic ingredient into microscopically small droplets, enabling better penetration of the ingredient into the epidermis. Currently this process has its limitations, but better systems may evolve in the future.

Aging of the skin should be considered in terms of chronological aging and solar aging.[4] Most of the changes we associate with skin aging are in fact a result of solar damage,

which produces wrinkling, loss of elasticity, variable pigmentation, and broken capillaries. Only creams that contain a sunscreen can be called "anti-aging." Nothing, except possibly creams containing retinoic acid, has been shown to reverse or prevent chronological aging. In the 1980s, a great deal of research was done to establish retinoic acid as an anti-aging cream. Creams containing collagen and elastin are occasionally promoted for their anti-aging or anti-wrinkle effects, but they have none. These are large molecules, incapable of penetrating the epidermal skin barrier to gain access to the dermis, where the aging process predominantly occurs.

Skin typing is a creation of women's magazines and people who sell cosmetics. There is no normal skin type. The oiliness or dryness of one's skin changes from day to day, even from hour to hour during the day.

The function of pores

Pores correspond to the ostium of hair follicles and eccrine sweat glands. They are static, and no cosmetic is capable of altering their size or shape. The need for toners or astringents seems to be generated by the desire to remove other skin care products, leading to the creation of a skin care routine.

There is a strict code of ethics governing the advertising of pharmaceutical and cosmetic products, but the cosmetic industry frequently bypasses this code by commissioning editorial comments in fashion magazines from poorly informed journalists. These comments are read uncritically by beauticians and sales representatives, who further perpetuate the inaccuracies.

Many products carry an endorsement by dermatologists or an institute of learning. My only personal experience with product testing, when I was a student at Oxford, involved the evaluation of a device to remove hair. The product claimed that its electronic tweezers could send an electric current down the hair follicle to the bulb and produce permanent hair destruction. We showed that the product did not do this and was no more effective than simply plucking hair, and we made this clear to the manufacturer. Nevertheless, I subsequently spotted an advertisement for the product, promoting it as being tested by dermatologists at Oxford University. Not surprisingly, the test results were not mentioned.

The science behind cosmetics is strong. There are abundant data on toxicology. Extensive work is done to develop a product that is better than its competitor in terms of touch, feel, and smell. After all, if the product is no good, then no amount of advertising will generate repeat sales. What is more questionable are the assumptions made by the cosmetic industry and the consumer: if you use moisturizers then you may need a skin care routine, incorporating toners and astringents to remove them. In the end, it is all consumer-driven. Cosmetics are luxury items, designed to make the user feel better, irrespective of whether they have any lasting impact on the skin.

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PRACTICE POINT
Beastly handwriting

It has long been a widely accepted fact—especially among patients, nurses, and pharmacists—that physicians have far worse handwriting than most other so-called learned professionals. Recent studies have largely confirmed this popular belief, one such study (1979) finding that 16% of doctors wrote quite illegibly and that the handwriting of another 17% was barely legible.

Why doctors should write so badly is not quite clear, and it is improbable that they are still trying to keep secret the contents of their prescriptions. Even more implausible explanations are defective toilet training and a collective "Disorder of Written Expression" (code 315.2). It is more likely that poor handwriting is caused by bad habits acquired while taking lecture notes in medical school, by excessive modern documentation requirements, or by just being too plain busy.

Good handwriting in the old days was achieved with ink-dipping pens that smudged the paper and stained the fingers. Even fountain pens, though invented around 1884, were thought to be incompatible with a neat hand, and ballpoints were definitely the devil's invention. Many graduates nowadays eschew even these satanic instruments, having typed their essays in college or used laptops ever since their days in playpens. Accordingly, a neat hand has become a rare phenomenon. In hospitals, even clinical clerks, once proud of their elegant notes, now scribble unconscionably, as do their chiefs.

Illegible writing, as everybody knows, may result in dreadful medical mishaps. While the future may well belong to computers and word-recognition transcription machines, several institutions have in the meantime tried to improve matters by offering remedial penmanship classes. Handwriting specialists have sprung up like mushrooms. Some have their own websites, and some are advising a change from the cursive baroque to the loop-free italic handwriting style with letters largely separate rather than joined. Others recommend going back to fountain pens, which tend to slow one down and thereby improve legibility.

Last year on impulse I bought such a device: a nonrefillable disposable fountain pen. I have used these pens ever since, and I also gave some to a colleague badly in need of them, with quite good results. I must say that, unfortunately, the clip tends to break off rather easily. Nevertheless, I can recommend these pens highly as a modest means of achieving an extra modicum of legibility.

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CLINICAL EVIDENCE

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Tuberculosis

QUESTIONS: What are the effects of different treatment regimens in people with newly diagnosed pulmonary tuberculosis? What are the effects of different drug regimens in people with multidrug-resistant tuberculosis? Which interventions improve adherence to treatment?

INTERVENTIONS

Beneficial

World Health Organization (WHO) short-course treatment (see glossary)
Antituberculous prophylaxis in people with HIV infection

Likely to be beneficial

Intermittent short-course treatment
Staff training, prompting mechanisms, enablers/cash incentives, health education, and directly observed treatment

Unknown effectiveness

Regimens containing quinolones
Comparative benefits of different regimens in multidrug-resistant tuberculosis
Sanctions for nonadherence to treatment

Likely to be ineffective or harmful

Treatment for less than 6 months

DEFINITION

Tuberculosis is caused by *Mycobacterium tuberculosis* and can affect many organs. Specific symptoms relate to the site of infection and are generally accompanied by fever, sweats, and weight loss.

INCIDENCE/PREVALENCE

About one third of the world's population is infected with *M tuberculosis*. The organism kills more people than any other infectious agent. The World Health Organization estimates that 95% of cases occur in developing countries and that 25% of avoidable deaths in those regions are caused by tuberculosis.[1]

ETIOLOGY

Social factors that increase risks include poverty, overcrowding, homelessness, and inadequate health services; medical factors include infection with HIV and immunosuppression.

PROGNOSIS

The prognosis varies widely and depends on treatment.[2]

AIMS

To cure tuberculosis, eliminate the risk of relapse, reduce infectivity, avoid emergence of drug resistance, and prevent death.

OUTCOMES

M tuberculosis in sputum (smear examination and culture); symptoms; weight; rates of relapse.

METHODS

We searched MEDLINE from 1966 to 1998 (key words: tuberculosis, pulmonary; trial, randomized controlled trial, controlled trial; isoniazid, pyrazinamide, rifampicin). We included all Cochrane systematic reviews, studies that were randomized or used alternate allocation, studies that had over 300 patients, and studies that had at least 1-year follow-up after completion of treatment.

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Summary Points

- Randomized controlled trials (RCTs) have found no differences in relapse rates between standard WHO short-course chemotherapy (6 months) and longer-term chemotherapy (8 to 9 months) in people with pulmonary tuberculosis. Use of pyrazinamide in the first 2 months seems to speed up sputum clearance but makes no difference in relapse rates. Extending its use beyond the first 2 months confers no additional benefit.
- We found limited evidence suggesting that there is no difference between daily and thrice-weekly short-course regimens. Reducing the duration of treatment from 6 to 4 months results in higher relapse rates.
- We found no good evidence comparing regimens containing quinolones with existing regimens.
- We found no good evidence comparing different drug regimens for multidrug-resistant tuberculosis.
- We found limited evidence suggesting that adherence to treatment may be improved by staff training, prompting mechanisms, enablers and cash incentives, health education, and direct patient observation. Sanctions for nonadherence to treatment have not been adequately evaluated.
- We found one RCT comparing the effect of directly observing patients while they take their treatment with allowing self-treatment at home. Nonrandomized tuberculosis strengthening programs, which include direct observation, have found improved adherence.

Glossary
WHO short-course chemotherapy includes 6 months of treatment, with 4 drugs in the first 2 months (isoniazid, rifampicin, pyrazinamide, and either ethambutol or intramuscular streptomycin), and 2 drugs in the subsequent 4 months (rifampicin and isoniazid).

QUESTION: What are the effects of different drug regimens in people with newly diagnosed pulmonary tuberculosis?

OPTION: SHORT-COURSE CHEMOTHERAPY

RCTs found no difference in relapse rates between WHO short-course chemotherapy (6 months—see glossary) and longer-term (8- to 9-month) chemotherapy in people with pulmonary tuberculosis. Use of pyrazinamide in the first 2 months was found to speed up sputum clearance but made no difference to relapse rates. Extending the use of pyrazinamide beyond the first 2 months conferred no additional benefit.

Benefits

We found no systematic review. Two RCTs published in the mid-1980s compared 6 versus 8 or 9 months' chemotherapy in a total of 1295 people with untreated culture- or smear-positive pulmonary tuberculosis.[3,4] Participants were followed up for at least 1 year after treatment was completed. The trials, performed in the United Kingdom and in east and central Africa, used different combinations of isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide for initial (first 2 months) and continuation treatment. Overall, there was no significant difference between short-course and longer regimens. Extending the use of pyrazinamide beyond the first 2 months did not improve cure rates. Sputum conversion was faster with regimens containing pyrazinamide, but there was no difference in relapse rates at 3-year follow-up.[4] There was no difference between regimens using ethambutol or streptomycin as the fourth drug in the initial phase.[4] A 6-month regimen using rifampicin and isoniazid throughout was highly effective (relapse rate, 2%) and was significantly better than isoniazid used alone in the 4-month continuation phase (relapse rate, 9%). When use of isoniazid alone was prolonged in a 6-month continuation phase, the relapse rate was not significantly better than with 4-month continuation.[3]

Harms

In the largest trial, possible adverse reactions were reported in 24 of 851 patients (3%), with only 6 requiring modification of treatment.[3] Two patients in this study developed jaundice, 1 of whom died.

Pyrazinamide

Adding pyrazinamide did not increase the incidence of hepatitis (4% with and without pyrazinamide).[4] Mild adverse effects were more common, however, including arthralgia, skin rashes, flu-like symptoms, mild gastrointestinal disturbance, vestibular disturbance, peripheral neuropathy, and confusion. Arthralgia was the most common adverse effect, reported in about 0.7% of patients on pyrazinamide,[3,4] but symptoms were mild and never required modification of treatment.

Comment

In patients who have been previously treated, the organisms may have acquired drug resistance, so WHO short-course chemotherapy may not be effective.

OPTION: INTERMITTENT DOSING

The limited data we found provide no evidence of a difference between daily and thrice-weekly short-course regimens but do not exclude a clinically significant difference.

Benefits

One systematic review published in January 1999 identified 1 RCT comparing 3 times per week versus daily chemotherapy for 6 months in 399 people with newly diagnosed pulmonary tuberculosis.[5] At 1 month after treatment was completed, there was no significant difference in rates of bacteriological cure, defined as negative sputum culture (99.9% vs 100%), or in relapse (5 patients vs 1 patient). At least 12 cohort studies have found cure rates of 80% to 100% with thrice-weekly regimens taken for 6 to 9 months.[5]

Harms

Intermittent treatment has the potential to contribute to drug resistance, but this was not shown in these studies.[5]

Comment

The number of people randomly allocated was too small to exclude a clinically significant difference between the dosing regimens.

OPTION: CHEMOTHERAPY FOR LESS THAN 6 MONTHS

We found limited evidence suggesting that reducing the duration of treatment to less than 6 months results in unacceptably high relapse rates.

Benefits

We found 1 systematic review that included 7 RCTs published between 1979 and 1989 on outpatients with newly diagnosed pulmonary tuberculosis.[6] The trials randomly allocated 228 and 2020 people in India, Hong Kong, Singapore, and Germany, comparing a variety of shorter (minimum 2 months) and longer (maximum 12 months) drug regimens. Relapse rates were consistently higher after the shorter duration treatments.

Harms
There was little difference in adverse events or toxicity except in 1 trial, which found that patients given a 2-month regimen were less likely to change or discontinue drugs than those given a 12-month regimen. Numbers, however, were small (6/299 vs 17/299).[6]

Comment
The treatments were given under ideal conditions. In clinical practice, relapse rates with shorter regimens are likely to be worse.

OPTION: REGIMENS CONTAINING QUINOLONES
Regimens containing quinolones have not been adequately compared with existing regimens in people with tuberculosis.

Benefits
We found no systematic review. One RCT of 200 patients from Tanzania found no significant difference in the rate of treatment failure between a regimen containing ciprofloxacin and a regimen not containing it (RR of relapse at 6 months 16, 95% confidence interval [CI] 0.94 to 278).[7] A relatively low dosage of ciprofloxacin was used (750 mg daily).

Harms
None reported

Comment
Quinolones have good bactericidal activity in vitro. Some of the newer quinolones have enhanced anti-mycobacterial activity compared with ciprofloxacin.

QUESTION: What are the effects of different drug regimens in people with multidrug-resistant tuberculosis?

Different drug regimens for multidrug-resistant tuberculosis have not been adequately compared.

Benefits
We found no systematic reviews and no RCTs comparing different regimens in people with multidrug-resistant tuberculosis.

Harms
Insufficient data

Comment
Current clinical practice in multidrug-resistant tuberculosis is to include at least 3 drugs to which the particular strain of tuberculosis is sensitive, using as many bactericidal agents as possible. Patients are directly observed and managed by a specialized clinician.

QUESTION: Which interventions improve adherence to treatment?

OPTION: STAFF TRAINING
We found limited evidence suggesting that training of health staff improves adherence.

Benefits
We found 1 systematic review, updated in November 1998,[8] which identified 1 RCT that compared intensive staff supervision with routine supervision at Korean centers performing tuberculosis extension activities. Centers were paired and randomized. Supervision was carried out by senior doctors. Higher completion rates were achieved with intensive supervision (RR 1.2, confidence intervals not yet available as cluster effect not yet corrected for).

Harms
None reported

Comment
The effect on adherence was modest, and we cannot yet say whether it was significant.

OPTION: PROMPTING MECHANISMS
RCTs have found that prompting mechanisms improve adherence.

Benefits
We found 1 systematic review that identified 2 RCTs.[8] The first compared reminder cards versus usual follow-up in people who did not collect their drugs after discharge from hospital. Those in the intervention group were more likely to complete their treatment (RR 1.2, 95% CI 1.1 to 1.4). The second trial, in the United States, compared the use of peer health advisers who met participants and went to the clinic with them. It found that there was increased attendance at the first follow-up appointment (RR versus no intervention 1.4, 95% CI 1.1 to 1.8).

Harms
None

Comment
Both were small studies from which it is not possible to generalize widely. Implementing prompting mechanisms in larger populations would require well-staffed and well-organized tuberculosis programs. It is not known whether the same effects would be observed in regional or national programs.

OPTION: ENABLERS
RCTs have found that cash incentives improve adherence among people living in deprived circumstances.

Benefits

We found 1 systematic review that identified 2 RCTs, both from the United States.[8] One, among homeless men, found that money ($5) improved attendance at the first appointment (RR 1.6, 95% CI 1.3 to 2.0). The other, among migrants, found that combining cash ($10) with health education improved attendance compared with usual care (RR 2.4, 95% CI 1.5 to 3.7).

Harms

None measured

Comment

None

OPTION: HEALTH EDUCATION

The effects of health education alone on adherence have been poorly evaluated in the limited evidence we found.

Benefits

We found 1 systematic review that identified 1 RCT, conducted in the United States,[8] comparing education by a doctor at a clinic versus giving the participant a leaflet. It found no significant difference in the proportion of participants completing treatment, although numbers were small.

Harms

None measured

Comment

The trial was probably too small to exclude an effect of health education. Other RCTs have evaluated health education as part of a motivational package, such as nurses phoning patients every 3 months. Its inclusion in a more complex package makes it difficult to evaluate the effects of education alone.

OPTIONS: SANCTIONS

Sanctions for failure to adhere to treatment have not been adequately evaluated in the evidence we found.

Benefits

We found 1 systematic review, but it identified no RCTs of sanctions.[8]

Harms

The use of sanctions may be ethically dubious because it reduces or removes a patient's choice.

Comment

In New York, the "locked hospital" was thought to have given credibility to the Department of Health's strategy for curing some patients.[9]

OPTION: DIRECT PATIENT OBSERVATION

One RCT has found that directly observing patients as they take their drugs makes little difference to adherence. Observational evidence, however, suggests that tuberculosis-strengthening programs, which usually include direct observation (often called directly observed therapy short-course programs or DOTs), can improve adherence.

Benefits

We found 1 systematic review that identified 1 RCT, conducted in South Africa, comparing direct observation of patients versus self-administered treatment at home.[8] It found no difference between the 2 strategies, although overall adherence in the study was low.

Harms

Potential harms include reduced cooperation between patient and doctor, removal of responsibility from patients, detrimental to long-term sustainability of anti-tuberculosis programs, and increased burden on health services to the detriment of care for other diseases. None of these has been adequately investigated.

Comment

Numerous observational studies have evaluated interventions described as DOTs, but all were intervention packages that included further anti-tuberculosis programs such as strengthening drug supplies, improving microscopy services, and offering numerous incentives, sanctions, and cointerventions likely to influence adherence.[10]

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TOOLBOX

Female sexual problems: loss of desire

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Loss of desire for sexual activity is the female sexual dysfunction most commonly presented. It is also often the hardest to treat. Much literature is available on female loss of desire. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), which gives our working classification of psychosexual dysfunction, would classify it as hypoactive sexual desire disorder and sexual aversion disorder. It has long been debated whether such a loss of sexual desire should be seen as abnormal or simply as a variation of normal.

Masters and Johnson's original "human sexual response curve" helps us understand loss of desire in the context of the normal sexual response. This diagrammatic representation describes increasing sexual pleasure against time—desire for sexual activity followed by arousal, orgasm, and finally resolution. It is important to remember, however, that the physiologies of desire, arousal, and orgasm are separate entities and therefore not dependent on each other. Women with a loss of desire (hypoactive sexual desire disorder) can have good sexual functioning. In essence, they will not initiate sexual contact.

Is desire a thought or a feeling? The answer is not clear. Certainly, early in loving relationships, physical arousal closely follows any sexual thought. We have a sexual thought, which then facilitates the arousal mechanism through neurological pathways. The thought could be anticipation of the evening ahead or a memory of a previous sexual encounter. Women who do not desire sexual activity can operate quite well sexually once engaged in the sexual encounter. Touch around the clitoris and genital area facilitates neurological pathways, producing good arousal and good lubrication, moving on to orgasm.

Possible causes of hyperprolactinemia

- Pituitary tumors
- Hypothyroidism
- Cirrhosis
- Stress
- Hypothalamic disease
- Hepatic disease
- Breast surgery
- Drug treatments

Illnesses that may result in a loss of sexual desire

- Gynecological disorders causing pain on sexual intercourse
- Obstetric disorders causing pain on sexual intercourse
- Urological disorders causing pain on sexual intercourse
- Alcohol and substance misuse
- Stress and chronic anxiety
- Endocrine disorders
- Neurological disorders
- Psychiatric disorders
- Depression
- Fatigue

CAUSES OF LOSS OF DESIRE

Much research into sexual desire is now underway, but the subject is still poorly understood. We know that certain medical conditions affect sexual desire. Depressive illness, for example, often dramatically reduces it, as do stress and fatigue.

Organic causes

Testosterone has a part to play in women's sexual desire, although much smaller amounts are required than in men. In women, testosterone production is split evenly between the ovaries and the adrenal gland. Androgen deficiency syndrome should be considered after hysterectomy and bilateral salpingo-oophorectomy and after chemotherapy for cancer, when treatment with testosterone can improve loss of desire. Conditions and drugs that cause hyperprolactinemia have a direct effect on reducing sexual drive (see box).

The effect of changing hormone patterns at different life stages is poorly understood, but it is well known that loss of desire is more common with premenstrual tension, in the postnatal period, and around menopause. Many drugs can also cause loss of desire. Loss of desire can also be secondary to poor sexual arousal and lack of orgasm (see box).

Any health problem that might affect sexual anatomy, the vascular system, the neurological system, and the endocrine system must be considered. Indirect causes are conditions that can cause dyspareunia; conditions that cause chronic pain, fatigue, and malaise; and conditions that interfere with the vascular and neurological pathways.

Psychological causes

It is often difficult to disentangle organic possibilities from the psychogenic variables in women at different life stages that affect

Drugs that can affect women's sexual function

- Anti-androgens
  - Cyproterone
  - Gonadotropin-releasing hormone analogs
- Anti-estrogens and other hormones
  - Tamoxifen
  - Contraceptive drugs
- Cytotoxic drugs
- Psychoactive drugs
- Sedatives
- Narcotics
- Antidepressants
- Neuroleptics
- Stimulants

Tony Stone Images

Loss of desire is part of the normal female sexual response.

how they see sexuality fitting into their lives. It is important to consider these points and not to allow ourselves to be dragged into the medical model. We should look at the importance of the different roles that women have in their lives and how they prioritize them.

Many women have several roles—the professional or worker, housewife, mother, daughter, friend, and lover. This last role seems to fade away as the demands of the others increase. When a woman meets her first serious partner, she has fewer of these other roles. She may be only a worker and a daughter. In later years, she will have more roles to contend with. She may be a mother and housewife as well. For many women it seems that as the responsibilities of other roles increase, the importance of the lover role diminishes.

Looking at these issues can be quite revealing. One way to give structure to this interpretation is to undertake a process that we can call the "timetable of life." Both partners in the relationship are asked to fill in a timetable representing a typical week. They are then asked to look at the week in terms of time spent in different categories: family time (that is, with children and partners), work time (both at work and work in the house), extended family time (with parents and relations), social time, personal time, and relationship time (time spent together alone, as a couple). This last category is, of course, the time when sexual activity is most likely to be realized successfully.

A timetable almost always shows that the elements missing are relationship time and personal time. Roles are, of course, not only about the practicalities of who does what but also about how a woman feels about her responsibility for the roles she takes on.

Sexual learning

It is useful to ask a woman about her experiences of learning about sexuality and their influence in the development of her sexuality. Sexual learning and role prioritization are often intertwined. An example of this is the woman who found that she had lost sexual desire after the birth of her first child. Discussion showed that she had, not unnaturally, made the responsibility of being a mother a high priority, but coupled with this was the clear message that she had received when learning about her sexuality that "mothers are not sexual beings."

Many misunderstandings and myths can be acquired during learning about sexuality: for example, a man is always ready and able to have sex; sex is natural and spontaneous; and sex equals intercourse. Sexual myths are held by women as well as men (see box).

It is useful to repeat the "timetable" for different times in a woman's life, comparing it during courtship, when sexual desire was probably high, with the times when sexual desire was low. This study shows how priorities change and how these changes can influence the desire for sexual activity.

Looking at what happens in a sexual situation often gives much information about the defenses erected when a patient engages in sexual activity. We can look at what turns a patient on and off, how absorbed she becomes in the sexual experience, whether loss of desire occurs on every occasion, or whether it is situational. Discussing other topics, such as sexual fantasy, masturbation,

Mother & Baby Picture Library

As a woman takes on the roles of mother and housewife, the importance of her role as lover may diminish.

Ten myths about sex

- In general, a man should not express certain emotions
- In sex, as elsewhere, it is performance that counts
- An erection is essential for a satisfying sexual experience
- All physical contact must lead to sex
- Sex equals intercourse
- Good sex must follow a linear progression of increasing excitement and terminate in orgasm
- Sex should be natural and spontaneous
- On the whole, the man must take charge of and orchestrate sex
- A man wants and is always ready for sex
- We no longer believe the above myths

Adapted from Zilbergeld B. Men and sex: a guide to sexual fulfilment. London: HarperCollins, 1995.

genital functioning, and contraception can also give great insight.

TREATMENT OPTIONS

An integrated approach to medical and psychological treatments is optimal. Any medical elements of the problem, if present, must be treated to achieve a positive outcome. In secondary loss of desire for sexual activity, a psychogenic aspect often remains after the medical elements have been treated (see box).

Most of the treatment will involve cognitive behavioral approaches and psychodynamic approaches, based on the discussions previously described. One of the most difficult areas to approach and affect is loss of attraction for the partner, which can lead to serious difficulties and have serious consequences.

Diagnostic checklist for women's loss of sexual desire

- Physical illness
- Integrity of anatomy
- Integrity of vascular system
- Integrity of neurological system
- Integrity of endocrine system
- Drugs and treatments
- Psychological characteristics
- Relationship issues
- Life changes
- Sexual history
- Sexual knowledge
- Attraction to partner

Callipygous Eve and Adoring Adam (1510) by Albrecht Dürer

We expect our partners to feel the same as we feel and to know when we feel sexual.

Working with the couple when there is loss of sexual desire allows both partners' understanding of the problem to be examined by some of the techniques above. As partners begin to realize that they can no longer assume that they know how their partner feels, or should feel, the differences in sexuality and sexual needs can be explored. We expect our partners to feel the same as we feel and to know when we feel sexual. We expect them to be able to provide for our needs sexually without necessarily discussing them. With counseling, the aim is to encourage acceptance of differences, a concept sometimes described as "benign variation."

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"Frigidity" is not featured in this discussion nor is it featured in any classification of female sexual dysfunction. The term is more a reflection of women's feelings about themselves or of men's feelings about women. When a woman describes herself as frigid, she is really describing how she feels about herself as a sexual being and is often comparing her feelings and behavior with her own or others' expectations of how she should feel. Because frigidity is not a medical term, we should no longer use it.

capsule

Baby boom could follow banning abortion Using data from the 1970s, when abortion was first made legal throughout the United States, the American Journal of Public Health predicts the consequences of recriminalizing abortion. The calculations suggest that as many as 444,000 extra babies could be born each year.

capsule

Head injuries may very rarely cause Parkinson's disease? Whether or not a single head injury can cause Parkinson's Disease has been debated for nearly 200 years. A case report in the Journal of Neurology, Neurosurgery and Psychiatry (1999:66;380-385) shows how magnetic resonance imaging was able to identify infarction of the left caudate nucleus extending into the lentiform nucleus in a patient who had developed signs of Parkinson's disease within six weeks of a head injury in a traffic accident.

Tuberculosis in Seattle, 1949-1973: balancing public health and civil liberties

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Summary Points

- American health officials have forcibly confined nonadherent tuberculosis patients throughout the 20th century.
- The country's most aggressive detention program after World War II was at Seattle's Firland Sanatorium.
- Although Seattle officials overused detention, they believed it was the only available mechanism for curing alcoholic tuberculosis patients from the city's "Skid Road."
- Modern tuberculosis workers caring for poor tuberculosis populations should not rely on coercion as a strategy for improving nonadherence.

Until the late 19th century, most physicians believed that pulmonary tuberculosis, then known as consumption, was not communicable. In 1882, however, the German scientist Robert Koch demonstrated otherwise. Tuberculosis, Koch proved, was caused by a bacterium, subsequently named *Mycobacterium tuberculosis*, which was transmitted to uninfected individuals via the pulmonary secretions of those sick with the disease.[1] Building on this knowledge, physicians and lay people throughout the United States inaugurated a tuberculosis control movement designed to prevent the spread of the disease.

Almost immediately, however, health officials realized that tuberculosis patients did not always follow sanitary regulations. In particular, many refused to remain in isolation hospitals, even if they were infectious. Such individuals were generally poor and often had multiple social problems. This paper will examine one such group—Skid Road alcoholics in Seattle, Washington—in the decades after World War II. (The place named "Skid Road" gave rise to the more common term "skid row.") Confronted with the perennial challenge of balancing the protection of public health with the rights of tuberculosis patients, Seattle officials established a locked ward at the local Firland Sanatorium in 1949. The history of detention at Firland demonstrates the challenges of trying to improve adherence among disadvantaged populations.

After a brief increase in the early 1990s, rates of tuberculosis in the United States are once again declining, but the disease remains epidemic in the developing world, where it causes millions of deaths each year. As officials confront the global threat of tuberculosis, it is instructive to review the history of Firland's locked ward. As in the past, the treatment of tuberculosis remains intertwined with the social problems that predispose poor people to the disease.

Special Collections, University of Washington Libraries, Neg. #UW6562.

Seattle in the time of tuberculosis.

Control programs begin

Building on Koch's work, New York City health officer Hermann Biggs organized America's first tuberculosis control program in 1893. National efforts began in 1904 with the founding of the National Association for the Study and Prevention of Tuberculosis, later the National Tuberculosis Association (NTA). Both Biggs and the NTA conducted campaigns designed to control the spread of tuberculosis, which preferentially affected crowded urban population centers. Educational materials urged citizens to lead healthy lifestyles, to cough into handkerchiefs, and never to spit in public.[2-5] Health officials also insisted that individuals with active tuberculosis remain isolated, either in tuberculosis sanatoriums or at home. As tuberculosis was the leading cause of death in many American cities in the early 20th century, such measures received wide support.

Treatment for tuberculosis during this era was largely supportive, consisting of fresh air and bed rest. Cures, when they occurred at all, frequently took months or years. As a result, against advice, patients often left hospitals prior to completing treatment. These individuals, mostly men, generally came from poor areas such as New York's Bowery district or Seattle's Skid Road. Their rates of alcoholism, homelessness, and unemployment were high.

One person who had little tolerance for unapproved discharges was Hermann Biggs. In 1903, he converted a portion of New York's Riverside Hospital into a detention facility. Biggs's decision to detain nonadherent consumptive patients was fully supported by state quarantine laws that permitted the detention of infectious patients believed

to be hazards. Yet the actual use of detention at Riverside did not only reflect public health concerns. "Homeless, friendless, dependent, dissipated and vicious consumptives," Biggs wrote in justifying his detention policies, "are likely to be most dangerous to the community."[6] This kind of language, commonplace among Biggs's contemporaries,[7] demonstrates how the actual danger these men represented became conflated with the public's largely negative assessment of their lives. As a result, the attempt to implement strict but fair public health policies in New York was subsumed by the perceived need to control an unruly population of alcoholics and vagrants.[8]

Despite Biggs's early efforts, American health departments actually used forcible detention quite sparingly during the first half of the 20th century. Detention was expensive and difficult to enforce, and it had no endpoint.[9] Tuberculosis officials in this era paid more attention to controlling populations than policing specific individuals. This situation would change dramatically after World War II with the introduction of the first curative antibiotics for tuberculosis. Streptomycin was introduced in 1947, followed by para-aminosalicylic acid in 1949 and isoniazid in 1952.[10] For the first time, detention of nonadherent persons, if needed, would only be required for a finite period.[11]

Nevertheless, health officials did not anticipate that they would have to rely extensively on forcible detention. They initially believed that tuberculosis patients would willingly take the new medications as prescribed. Yet antibiotics proved to be no panacea. Many patients still left sanatoriums against advice and did not regularly take their pills after discharge. At times, such nonadherence led to the development of drug-resistant strains of tuberculosis. Confronted anew with Biggs's dilemma of balancing public health and civil liberties, health departments once again turned to detention as a way to make patients comply.

Between 1945 and 1970, more than 30 states forcibly detained tuberculosis patients. These efforts varied widely. Most health departments confined patients in locked hospital wards, but some used prisons.[11] Certain states required extensive legal proceedings prior to detention, while others gave public health officials broad discretionary power. If there was a prototypical detention program anywhere in the country, however, it was at Firland.

Sequestered in Seattle

How did Seattle implement its isolation policies? First, Washington state tuberculosis control officer Cedric Northrop made sure that regulations carefully spelled out the exact powers of public health officers. In 1948, Northrop drafted an ordinance enabling the Seattle health officers to quarantine to Firland anyone with active tuberculosis who was "uncooperative" and "refused to observe the [necessary] precautions to prevent the spread of the disease."[12] Those quarantined were to remain until discharge was approved.

When early efforts at quarantine did not prevent discharges against advice, Firland, in June 1949, established a 27-bed locked ward. Known as Ward 6, the unit was equipped with both locked doors and heavily screened windows (Figure 1). All admitted patients spent the first 24 hours in a locked cell, which contained only concrete slabs covered by thin mattresses (Figure 2).[13-15] Firland staff planned to use Ward 6 sparingly. "If coercion is needed frequently," medical director Roberts Davies wrote, "it is a sure sign that something is wrong."[16] In fact, the early use of Ward 6 was limited. Northrop observed in December 1949 that it housed "only a handful" of patients. There were no beds for women.[17]

Over time, however, this situation changed. Initially, Northrop had planned to use forcible isolation for the occasional nonadherent person in the community who represented a public health threat. It soon became clear that the major problem in tuberculosis control was occurring at the sanatorium itself among a specific population of patients: so-called Skid Road alcoholics. These men, transients who traveled the West Coast looking for jobs, lived in an area south of downtown Seattle known as the Skid Road.[18] Their tuberculosis rates were the city's highest.

What problems did these men create at Firland? First, many of them went AWOL from the sanatorium for variable periods of time, often returning drunk. In addition, although possession of alcohol at Firland was illegal, bootlegger patients frequently smuggled in large quantities of liquor. Loud, raucous drinking parties often ensued in Firland's unlocked areas.[13]

While the behavior of Skid Road alcoholic patients caused much frustration, Firland did not simply respond in a punitive manner. Its staff was committed to the care of alcoholics and treated them with more tolerance and respect than they received in jail or in public hospitals. In addition, by the

Photograph by author, 1993

Figure 1 *Heavily screened windows on the outside of Firland Sanatorium's locked ward.*

early 1950s, alcoholism was being reclassified as a disease as opposed to a sin. In response, the sanatorium developed an extensive program of social and rehabilitative services, including programs that addressed issues of unemployment and alcoholism among Skid Road patients.[19]

Nevertheless, staff members grew increasingly concerned about the disorder that the Skid Road population caused at the sanatorium. As a result, they began to detain Skid Road alcoholics who went AWOL, overstayed a 24-hour pass, or got drunk at Firland. While Northrop's initial order of quarantine had stated that only patients with *active* tuberculosis could be forcibly isolated, this did not occur in practice. Firland staff also sent patients with *inactive* tuberculosis to Ward 6 for having gone AWOL or gotten drunk. These patients included those who had been noninfectious for 3 to 6 months and had always been totally compliant with their antibiotics. Basically, therefore, the disruption of institutional order at Firland came to be seen as a public health violation, punishable by detention.[11]

Decisions about which patients would be detained were made almost entirely at the sanatorium, without formal legal proceedings. The medical director decided which transgressions warranted punishment and how long detention would last. Generally, length of stay on Ward 6 followed a standard formula: the first stay was 2 weeks; the second, 1 month; and the third, 3 months.[13,14] Patients who repeatedly broke rules and required prolonged hospitalization often stayed on the locked ward for a period of time totaling several years. Few, if any, middle-class patients who broke rules at Firland were confined.

Photograph by author, 1993.

Figure 2 *One of the locked cells used for acutely inebriated tuberculosis patients at Firland Sanatorium. A thin mattress was placed on the concrete slab.*

Patients' objections

Most detained patients raised no objections. In a series of letters sent to government officials and the media in 1956 and 1957, however, several Firland patients registered complaints. One patient, for example, questioned why the health officer could quarantine noninfectious persons. "The patients themselves," the author wrote, "would be the first to condemn another who left here illegally if he were contagious; however, contagiousness has nothing to do with the quarantines."[20] Another patient asked why someone returning from a 24-hour pass after having "one or two drinks" was "treated as an alcoholic" and had a "very good chance of being thrown in jail."[21]

This same patient criticized the lack of formal legal input. The doctors, he wrote, "may sentence a patient from one day to six months, as they see fit. We want to know by what right, and on what authority this is being done."[21] "Free-born people," 2 patients proclaimed in 1957, "are not accustomed to dictatorship that forces indignaties [sic] on them while they are helpless."[22]

These complaints were generally greeted with skepticism. Health officials were particularly critical, terming the missives "typical 'crank' letters which we have been accustomed to seeing produced by the paranoid type of personality."[23] Eventually the patients' complaints reached the Washington chapter of the American Civil Liberties Union (ACLU). ACLU representatives who investigated conditions at the sanatorium in 1957 documented the following civil liberties "abuses" at Firland: "misuse of quarantine..., the assignment of patients to maximum security wards, and the use of solitary confinement."[24] Yet even the ACLU let the issue drop.

Once Firland turned to quarantine and detention to maintain order, the use of those measures increased markedly. Whereas 10% of patients had been quarantined in 1952, the figure reached 30% by 1960.[12] In 1954, Ward 6 expanded from 27 to 54 beds, including 6 beds for women.[15] By 1960, almost half of hospitalized Skid Road alcoholics were detained for at least 2 weeks.[25] Detention, initially intended for the occasional and extremely nonadherent individual, had become nearly standard management of Skid Road alcoholic patients.

Meanwhile, Firland's locked ward became a model for similar units across the country. Staff physicians wrote numerous articles on the management of so-called "recalcitrant" tuberculosis patients. Large numbers of people,

wrote medical director Thomas Sheehy, Jr., in 1957, "come to Firland from all points around the country to observe Ward Six in action."[26] For the most part, national commentators condoned detention. For persistently obstinate patients, wrote the Journal of the American Medical Association in 1958, it was necessary to "resort to available legal measures."[27] One physician who objected to forcible confinement was Denver's Sidney Dressler, who termed detention a "misapplication of police authority" that led health officials to treat patients like criminals.[28]

By the mid-1960s, growing legal challenges to the civil commitment of the mentally ill had begun to have repercussions at Firland. In 1964, the ACLU returned to the sanatorium to establish a unique program in which a Seattle district court judge traveled to Firland to hear the grievances of detained patients.[19] Staff members became more tolerant of misbehavior at the institution. Indeed, at times, Ward 6 was a subject of humor, as in this poem from Firland's patient magazine:

> No matter what I do "for kicks,"
> I'm always ending up in "6,"
> As anyone can plainly see,
> This must be where I like to be.
> The keys and locks could go—it's true,
> And heavy screens don't help our view.
> But if in "6" I have to stay,
> My friends are with me—anyway.[29]

Similarly, an advice column in the magazine, entitled "San Landers," offered droll counsel to detainees. Despite the more flexible environment, Firland continued to confine nonadherent individuals until it closed in 1973. Between 1949 and 1973, the sanatorium detained close to 2000 patients.

As with Hermann Biggs's policies in New York, it is easy in retrospect to criticize Firland's excessive use of detention. What should be emphasized, however, is the manner in which public health work once again became conflated with the need to control a "difficult" patient population. Seattle officials were careful to update and clarify their quarantine regulations before initiating detention. They planned to use detention only as a last resort. They took rehabilitation of the alcoholic patient quite seriously. Nevertheless, in practice, public health powers were inappropriately stretched.

Conclusion

Lacking conclusive studies, it is difficult to ascertain the degree to which coercion of tuberculosis patients contributed to the declining rates of the disease from the 1950s to the mid-1980s. Yet when tuberculosis underwent a resurgence in the United States beginning in 1985,[30] including highly lethal multidrug-resistant (MDR) strains, health officials again recommended the use of forcible detention to help control the disease. Given that the return of tuberculosis was linked to issues such as nonadherence, homelessness, and HIV infection,[31,32] such a response is not surprising. Health departments established detention programs in New York City, Denver, Massachusetts, and California, among other locations.[33-36]

Fortunately, modern tuberculosis officials have been careful to use such powers sparingly, confining from 1.3% to 5% percent of their patients. Building on court decisions from the 1960s and 1970s, those detained have had access to legal representation and other due process protections.[37,38] In general, health departments have detained persons only when they have failed other "least restrictive alternatives." Foremost among these is directly observed therapy (DOT), in which outpatients take antibiotics in the presence of an outreach worker.

Yet the history of Firland should remind us of the ramifications of the use of forcible confinement. Although modern health officials have strived to use detention only for persistently nonadherent individuals, such persons almost invariably come from the poorest populations. Indeed, due to complicated sociomedical problems, such as psychiatric disorders and substance use, adherence may be an impossibility for such individuals. Society should not use coercion as a substitute for addressing the underlying causes of nonadherence.[39] Detention should also be a last resort for controlling tuberculosis among immigrants from the developing world, who have high rates of MDR disease.[40]

Indeed, it is in the developing world that the problem of tuberculosis remains especially acute. As the incidence of the disease has once again declined in Western nations, the vast majority of the roughly 3 million annual deaths from tuberculosis occur in poor countries in Africa, Asia, and Southeast Asia. Frequent coinfection with HIV makes tuberculosis extremely hard to control in these areas. Hoping to repeat the recent successes of DOT in the United States, health officials in these countries, working with the World Health Organization and other agencies, are aggressively promoting the widespread dissemination of so-called directly observed therapy short course (DOTs).[41] DOTs aims to control tuberculosis in low-income, high-prevalence areas with an intensive 6-month course of supervised antibiotic therapy. In this sense, public health efforts in the 21st century will harken back to the early attempts of Hermann Biggs to implement population-based strategies for preventing and treating tuberculosis among the highly susceptible urban poor.

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COMMENTARY

Considerations on the road to involuntary confinement

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Mr. Martinez came from the Philippines to San Francisco. He came with other 70-year-old veterans, naturalized citizens who had been promised a monthly social security check for supporting the Allies in World War II. He left behind his family and most of his material goods, but he brought along his drug-resistant tuberculosis. From late at night until dawn, he worked with other Filipinos, cleaning and completing odd jobs around the casinos in Reno, Nevada. By the time his illness was diagnosed, a few years after he arrived in the United States, he could no longer support himself or send money home.

Because his tuberculosis was drug-resistant, he was placed on directly observed therapy (DOT). He came into the clinic or met with someone at his home or in the neighborhood who would watch him take his pills. He said he was not an educated man and had trouble remembering his weekend dose of medications. While he did not mind the directly observed therapy, he needed his extra income and would leave for Reno once or twice a week.

The clinic staff was sympathetic but resolved to hold Mr. Martinez to the rigors of directly observed therapy. They had sent their Filipino health worker to educate him; they had offered him sandwiches, bus tokens, and kind words. Treating him through the tuberculosis clinic in Reno was not an option since he worked irregularly and at different places. He was a public health threat. What was left except to confine him involuntarily in the hospital or the jail?

Tuberculosis is the classic disease for observing the interplay between individual rights and public health protection. Directly observed therapy, implemented by skilled health workers and enhanced with incentives and enablers, is the primary tool for successful treatment of tuberculosis,[1] but it does not always work. Lerner has examined the evolution of confinement in Seattle, Washington, as a means of controlling tuberculosis.[2] Now, as then, while involuntary confinement appears the ultimate tool for successful treatment of tuberculosis, closer examination suggests that less coercive measures may be more suitable.

In the United States, public health emphasis has seesawed between chemotherapy and behavioral therapy. When new drugs for treating tuberculosis became available in the 1950s, behavioral interventions were shunted aside, only to reemerge as a critical tool with the new round of epidemics in the late 1980s. The rise in the number of people with the disease and the development of multidrug resistance, due primarily to poor therapy adherence, motivated changes in tuberculosis programs. Behavioral interventions, in the form of directly observed therapy, have been the treatment of choice since adherence seized the

agenda in the prevention and treatment of tuberculosis. While most patients respond to orders for directly observed therapy, many states revamped old public health laws to enforce treatment. Involuntary confinement is seen as the ultimate tool in treatment. In a systematic evaluation of involuntary confinement in California, however, 3 questions arose: How effective is coercion as a control measure for tuberculosis? Is it applied equitably across counties? How frequently available and utilized are less coercive measures, including comprehensive psychiatric and addiction care?[3]

Is involuntary confinement effective? In the study by Oscherwitz et al., 84% of confined patients eventually completed therapy although most were not forced to remain confined to the end of treatment. While this is a high percentage of treatment completion in a difficult group of patients, Centers for Disease Control guidelines call for 90% completion rates.[4] Even using the "ultimate tool" for control, success is not guaranteed.

Is involuntary confinement being equitably applied? Patients in the California study who were identified as needing involuntary confinement were more often young, homeless, and unemployed, with drug and alcohol histories, as compared with patients who were more adherent to therapy for tuberculosis. The rates of tuberculosis patients needing confinement varied widely by county. Some tuberculosis control officers reported attempting to confine no one; others confined up to 8.9% of their cases in the study years examined. Counties varied widely in their access to suitable places to confine contagious patients, in their relationships with the sheriffs and judges needed to implement and maintain confinement orders, and in their philosophy about the use of involuntary confinement.

Are control officers considering less coercive measures? Evaluation and treatment of comorbid illnesses might actually interfere with the ability to accept therapy for tuberculosis. Where substance misuse or mental illness was identified in nonadherent patients, fewer than half were documented as having been referred for care of these illnesses prior to their planned involuntary confinement.

The larger question of protection of rights is raised for tuberculosis patients who also suffer from mental illness or substance misuse. Is it fair to use threats such as involuntary confinement if the patient's ability to understand the consequences is impaired? The bacilli of the mentally ill patient may be just as contagious as the mentally well patient's. Are the rights of the former being upheld if he or she does not comprehend the connection between behavior and punishment? This question is particularly important when one considers the availability of routine mental health assessments by trained professionals in tuberculosis control programs. Few have access to staff that are trained in mental health assessment, and almost none are able to offer professional interventions on site.

Most publicly available mental health care comes from the same public health departments that fund tuberculosis control. There may be long waits for assessments. Access to ongoing treatment may be available only for the most seriously impaired. Access to drug and alcohol treatment programs is more available, but in many counties court orders are required to put patients at the top of the treatment waiting lists.

Are there options better than confinement? Positive-value incentives have been used widely, though casually, in most control programs. Programs rely on noncash incentives such as meals, vouchers for food, transportation assistance, an occasional birthday card, or flowers from the staff gardens to engage and reward patients. Studies of protocol-guided use of cash and noncash incentives are showing rates greater than 80% in completion of appointments to the tuberculosis clinic and completion of therapy.[5-7] Small cash incentives bring screening and preventive therapy completions to rates equal to the best efforts of highly skilled tuberculosis control programs that use conventional methods.[8] While none of these studies has compared cash incentives to the threat of or use of involuntary confinement as a tool for implementing directly observed therapy, there is clearly potential for less overtly coercive means of completing treatment.

The use of cash incentives for health care engenders much debate among public health specialists. The slippery slope of getting into the business of "paying to get healthy" looms large in the minds of all who contemplate the prospects of cash distribution at the local tuberculosis clinic. Would people try to get tuberculosis so they could be paid to take medication? If we pay for tuberculosis care, will we have to start paying people to take their pills for sexually transmitted diseases and AIDS? Where individual health and public health concerns overlap, these dilemmas are real.

While there are difficult ethical and social issues in the use of incentives, perhaps we must accept that in matters of individual rights and public health there are no easy fixes. If a "tuberculosis stipend" offers our Filipino veteran an incentive to stay home and comply with his directly observed therapy, and furthermore keeps him out of the locked ward in the county jail, which would you prefer to consider as the option of last resort?

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Narrative in medical ethics

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Narrative contributes to medical ethics primarily in 2 ways: first through the use of stories (or narratives) for their mimetic content—that is, for what they say—and second through analysis of diegetic form—that is, for the understanding of how stories are told and why it matters, viewed according to methods of literary criticism and narrative theory. Although narrative and narrative theory, like the form and content of a literary work, are inextricably bound up with each other, I will discuss each separately to chart the evolving appreciation of the importance of narrative in medical ethics.

Summary Points

- Narrative contributes to medical ethics through the content of stories (what stories say) and through an analysis of their form (how stories are told and why it matters).
- The study of both fictional and factual stories can aid understanding in medical ethics.
- The techniques of literary criticism can be applied to texts and practices to reveal different perspectives in a medical-ethical dilemma.
- To understand and accept a patient's moral choices, a practitioner must acknowledge that the illness narrative has many potential interpretations but that the patient is the ultimate author of his or her own text.

The use of stories

During the past 2 decades, stories have come to be seen as important to medical ethics in at least 3 ways: first, as case examples for the teaching of principle-based professional ethics, which has been the dominant form of medical ethics in the Western world; second, as moral guides to living a good life, not just in the practice of medicine but in all aspects of life; and third, as witness that, given the experiential truth and passion of narrative, medical practices and ethical precepts must be reexamined.

Stories as cases for teaching principle-based medical ethics

When medical humanities programs were first established in American medical schools in the 1970s and 1980s, historians, ethicists, and lawyers usually preceded scholars of literature on the faculty. In the early years, the presence of literature in medical humanities curricula was often justified by its service in the teaching of medical ethics.[1] Literary stories were useful in "fleshing out" issues or dilemmas in medical ethics by showing them embedded in a particularized human context, complicated by powerful emotions and complex interpersonal dynamics. Works by physician-writers have since then become staples of such teaching, and the short stories of Williams[2] and Selzer[3] are now well known and frequently taught.

Narrated retrospectively from the doctor's point of view, stories such as Williams' "The use of force"[2] and Selzer's "Brute"[3] offer insight into why a presumably good doctor with beneficent intentions nonetheless ends up harming his patient in an abuse of power.

These stories may first have been used as cases for limited discussions of standard ethical principles such as autonomy or respect for persons, beneficence and nonmaleficence, and social justice.[4] Principle-based ethics offers a further way of using such stories in teaching.

In principle-based ethics, or principlism, general ethical principles are applied in a deductive case analysis to determine logically the best ethical resolution of its issues or dilemmas.[5] In both "The use of force" and "Brute," a doctor physically assaults a patient in order to diagnose or treat. The ethical issue is whether such powerful medical paternalism can be justified by appealing to beneficence—that is, by claiming that what the doctor did was for the patient's own good. By attending to the richly evocative language used by the doctor-narrators of these stories, readers have the opportunity to learn about more than patients' autonomy and doctors' paternalism. They can learn how ethical principles and arguments may sometimes be used to rationalize unethical behavior that is driven by sexual attraction, anger, or pride.[6-8]

Although still controversial,[9-11] the use of such stories as literary cases to complement the teaching of principlism is the most basic way in which narrative has been important to medical ethics.

Narratives as moral guides for living a good life

The second way in which literary narratives have been important to medical ethics is best articulated by Coles, who is concerned with far-ranging moral inquiry that does not limit itself to the practice of medicine.[12] Coles is concerned with what it means to live a good life and, coincidentally, to practice medicine. He seeks to develop in his medical students not professional medical ethics but existential or virtue ethics. For this purpose, Coles believes that reading novels such as Eliot's Middlemarch, Lewis's Arrowsmith, Fitzgerald's Tender Is the Night, and Percy's Love in the Ruins works better than studying analytic ethics.

Although Coles chooses more complex literary texts than the short stories that are often used as cases for the teaching of medical ethics, he chooses novels whose main characters are doctors. Narratives that serve as moral guides for living a good life need not be topically about medicine, however, as Hawkins has argued in describing her use of

Dante's The Divine Comedy with medical students.[13] From this broader perspective, any narrative that might instigate moral reflection about what it means to be a good person, to live a good life, and to practice a profession ethically could be considered important for medical ethics.

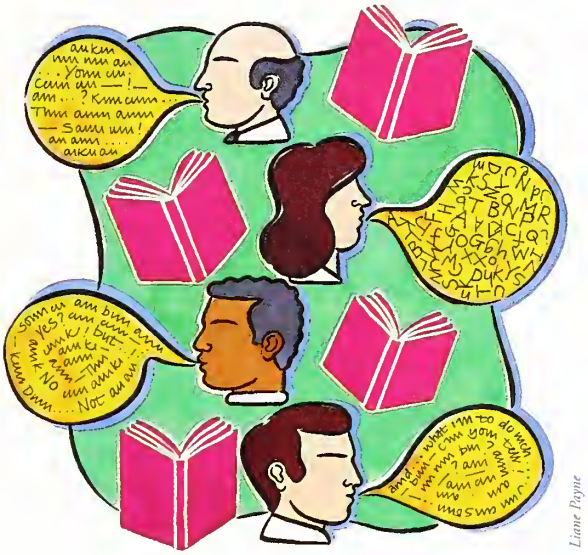
Narratives of witness

Autobiographical accounts by patients or their family members and friends can also be important for medical ethics as narratives of witness.[14] Some of these narratives comment from the patient's point of view on ethical issues such as autonomy and respect for persons, truth-telling and informed consent, beneficence (and, sometimes, maleficence or negligence), incompetence, and error. As these narratives have begun to appear on the Internet, they have reached larger audiences. They hold the potential for more influence on the practices of doctors and institutions.[15]

Patients and their family and friends are not the only ones who write important narratives of witness. By writing narratives from their personal experiences, doctors and other healthcare professionals also can have a powerful effect on the public discussion of ethical issues. In the United States, for example, it was doctors' narratives of assisting patients' suicides that broke through decades of professional silence and opened debate about this issue in the medical journals. In 1982, after Selzer published his fictional story "Mercy,"[3] about a doctor's unsuccessful attempt to help a terminally ill patient die by giving him an overdose of morphine, he received hate mail. A few years later, when the Journal of the American Medical Association published "It's over, Debbie"[16]—an anonymous, presumably factual account by a doctor who had deliberately given a patient, terminally ill with cancer, an overdose of analgesics to speed her death—a Cook County state's attorney took the journal editor to court, trying to force him to reveal the author's identity. The effort was unsuccessful. A few years later, after Quill published an eloquently written account of prescribing drugs for a patient who, he knew, intended to use them to commit suicide,[17] he was brought before a grand jury but not indicted. Despite the general legal prohibition against doctor-assisted suicide in the United States, exemplified by the legal action taken in both these examples, doctors' narratives have helped compel reexamination of this controversial ethical issue.

Narrative approaches to medical ethics

In the past decade, scholars have begun to use the methods of literary criticism and narrative theory to examine the texts and practices of traditional medical ethics. Now referred to as narrative approaches to medical ethics, or narrative contributions to medical ethics, these techniques use literary analysis to enhance a principle-based medical ethics practice. Narrative ethics has reconceptualized



Liane Payne

the practice of medical ethics, seeking to replace principlism with a paradigmatically different practice.

Early medical humanities programs in the United States justified the presence of literature in the curriculum on the basis of its service to medical ethics[1] or claims that literature teaches students "to read in the fullest sense,"[18] a skill that prepares them for the clinical work of listening to and interpreting patients' stories[19] as well as reconfiguring those stories as medical cases with plots and causality.[20] To read in the fullest sense, students must have mastered certain basic skills of literary analysis. The same questions that they learn to ask about a literary text can also be used in the examination of ethical texts and practices: Who is the narrator? Is the narrator reliable? From which angle of vision does the narrator tell the story? What has been left out of the narrative? Whose voice is not being heard and why? What kind of language and images does the narrator use? What effect do those narrative choices have in creating patterns of meaning?

One of the best examples of applying these methods to ethical texts is Chambers's work examining the inherent value biases in the ways that ethicists construct their cases.[21] Chambers shows that from their very first choices—of point of view, diction, images, and other features of style—ethicists construct cases that lead readers to the conclusions that emanate from the author's ethical theories and preferences.

Charon is the best-known advocate of the use of literary criticism and narrative theory to help doctors and ethicists examine their ethical practices. The title of her article, "Narrative contributions to medical ethics: recognition, formulation, interpretation, and validation in the practice of the ethicist,"[22] is in itself almost a summary of her position. Making doctors and ethicists more aware of the narrative aspects of their practices will make them better doctors and ethicists, she argues.[22] She hopes that narratively competent practitioners will have conversations

about ethics and values with their patients before a medical crisis throws them into an unanticipated dilemma.

Narrative ethics

Hunter's work on the narrative structure of medical knowledge has helped clarify some of the mental processes involved in medical education and practice.[20] Unlike analytic philosophers, who are trained to work deductively from general principles to the particular case, doctors are trained to work in the opposite direction, beginning with the particular case and then seeking general medical principles that might apply. Hunter argues that this practice is not inductive but abductive, as doctors tack back and forth between a particular case and the generalized realm of scientific knowledge,[20, 23, 24] a process similar to the ethical practice of casuistry, as revived in an influential book by Jonsen and Toulmin.[25] In casuistry, ethical examination begins with the features of a particular case, then seeks to recall similar paradigm cases that may provide enlightenment about the best resolution for the case at hand. Casuistry is, arguably, one form of narrative ethics.

But narrative ethics has underlying assumptions that casuistry does not share. Foremost among them is a focus on the patient as narrator of his or her own story, including the ethical choices within the story. Brody has described a narrative ethics in which the doctor must work as co-author with the patient to construct a joint narrative of illness and medical care.[26] This co-authoring involves more than simply recognizing the patient's autonomy as author. Brody calls it a relational ethic.[26] Kleinman[27] and Frank[28] have written about the experience from the perspectives of doctor and patient, respectively, but both agree that such a narrative practice is relational and requires the doctor to be an empathic witness of the patient's suffering.

In an ideal form, narrative ethics recognizes the primacy of the patient's story[29] but encourages multiple voices to be heard and multiple stories to be brought forth by those whose lives will be involved in the resolution of a case.[30, 31] Patient, doctor, family, nurse, friend, and social worker, for example, may all share their stories in a dialogical chorus[32] that can offer the best chance of respecting all the persons involved.[33]

To move narrative ethics into a next phase of development, proponents must determine how competence training might best be achieved. Reading and interpreting complex written narratives, as the field of literature and medicine has been doing for 25 years, certainly helps.[34] But for those whose professional training has not included such experiences, continuing education that focuses on specific narrative skills may be helpful.[35] Greater narrative competence may or may not make analytically trained ethicists more open to the possibilities of narrative ethics. Nevertheless, such training will do them no harm and it may lead to a richer ethical discourse for us all.

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In the Public Eye

Media Watch

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Medical and scientific research has become more complex and often more controversial. Local institutional review boards, regulated by the federal government, are meant to protect subjects and staff from negative consequences from participation in or proximity to research. What happens when safeguards for human or animal subjects become deficient? Who must take control to ensure safety?

The seriousness of these questions became apparent at the end of March 1999 when, after years of investigation and advisement, the Office for Protection from Research Risk issued a directive instructing the West Los Angeles Veterans Administration to suspend federally funded human research and deactivated their "assurance" (see box). CNN and other media reported that officials at the Los Angeles veterans hospitals had allowed potentially harmful research to be carried out on patients without their proper consent. A cardiologist was accused of conducting cardiac catheterization procedures without obtaining consent. CNN quoted Republican Terry Everett, chair of the House Veterans Affairs Committee's oversight and investigations panel, as saying, "The concerns about informed consent go straight back to the awful things the Nazis did to people during the Holocaust and called it medical research. The civilized world vowed it should not happen again."

What happened?

Initially VA researchers and the affiliated UCLA community were taken aback by the stringent ruling. To many, it seemed sudden and harsh. The letter from the Office for Protection from Research Risk, however, clearly stated that concerns over administrative deficiencies occurring over the past 6 years in the VA Greater Los Angeles Healthcare System had led to this action. The VA simply did not appear to be holding up its end of the assurance commitment. While the Office for Protection from Research Risk ordered that only federally funded human research should be stopped, another letter from Kenneth Kizer, M.D., undersecretary at the Department of Veteran Affairs, extended the suspension to animal research. Dr. Kizer also said that because West Los Angeles VA is part of a Multiple Project Human Subject Assurance, research at the entire VA Greater Los Angeles Healthcare System, including Sepulveda VA, would be suspended as a preventive rather than a punitive measure.

This suspension order meant that no new patients could be recruited and no additional animals could be purchased. Stipulations did allow existing treatments to continue if the cessation of a drug or procedure would pose a health risk to the subject. Nearly 6 years of correspondence between the Office for Protection from Research Risk and the West Los Angeles

What is an assurance?

An assurance with the Office for Protection from Research Risk is a formal written commitment to

1) widely held ethical principles
2) DHHS regulations for Protection of Human Subjects
3) institutional procedures adequate to safeguard the rights and welfare of human subjects.

Puglisi JT [testimony]. Subcommittee on Oversight and Investigations and Subcommittee on Health of the Committee on Veterans' Affairs (April 21, 1999).

VA document efforts by the latter to comply with the oversight agency's recommendations and provide evidence of progress. In July 1994, the Office for Protection from Research Risk placed a "restriction" on the West Los Angeles VA, requiring quarterly reports on the implementation of the recommendations, all of which had been based on Health and Human Services regulations.

The main concerns

The investigations and recommendations centered on appropriate informed consent as well as proper approval and review of research projects. The oversight agency offered suggestions for changes in the consent language. The language was thought to be too technical for the veteran population, and it was noted that many existing consent forms omitted basic elements required by Health and Human Services. In addition, proper disclosure of information to potential research participants, in particular those with impaired decisionmaking capacity, was not sufficiently detailed. Site visits found the VA lacking consent documentation, and there was no organized filing and tracking system for consent forms.

The role of the institutional review board

A research proposal cannot receive federal funding without approval from the institutional review board. To ascertain appropriateness and safety of a proposal, boards require a vote from a minimum of 5 people, including at least 1 scientist, 1 nonscientist, and 1 person not otherwise affiliated with the institution. To achieve a quorum, a nonscientist must be present.

Once research is approved and initiated, the institutional review board retains the responsibility of monitoring both the consent process and safety risks. The board can suspend or terminate a project if research is not being conducted in accordance with institutional review board requirements, or if it has been associated with unexpected serious risk to participants.

The Office for Protection from Research Risk reviewed minutes from 9 VA institutional research board meetings and found that 7 of those meetings lacked a quorum, rendering their decisions invalid. The office's request for board minutes to document the results of votes was also not heeded. Finally, the VA failed to secure a patient representative for the institutional review board.

AP Photo/Rich Pedroncelli

Saluting the flag during Veteran's Day ceremonies at Capitol Park in Sacramento. The public has been shocked at revelations about veterans' hospital treatment.

The VA's response

In a letter to medical colleagues in April, Dr. Gerald S. Levey, provost of the UCLA Medical Sciences and dean of the UCLA School of Medicine, wrote that the VA Greater Los Angeles Healthcare System affiliates "have had an outstanding track record of success in both clinical and basic research, and there is need not only to preserve that success [but also] to bring the institution to an even greater level of achievement by correcting many of the administrative deficiencies that existed at the WLAVA and at Sepulveda VA."

A new acting associate chief of staff for research, Marguerite Hayes, M.D., was detailed to the site to oversee the implementation of the directives from the Office for Protection from Research Risk and VA headquarters. High on the list of her charges was the reinstitution of legally and appropriately constituted institutional review boards.

At the West Los Angeles VA alone, over 750 research projects were underway at the time the suspension was initiated. Nearly 70 were nonhuman, nonanimal, nonbiohazard studies, and those were immediately released from the suspension. As of July, all animal studies and over 90% of biohazard studies had been released. For the human studies, the 3 reconstituted institutional review boards, using proper membership representation and approval procedures, must review each protocol. Once the institutional review board approves the protocol, the Office for Protection from Research Risk and VA headquarters must grant the final authorization to resume the study. Each government-funded study must apply for a "single project assurance" (SPA).

In May, J. Thomas Puglisi, director of Human Subject Protection at the Office for Protection from Research Risk, said that few single project assurances had been received. Of the over 400 human subject studies, 14% are government-funded, through NIH or the Department of Veterans Affairs. None of these government-funded projects has been released. Most of the 13% that have been released are funded by pharmaceutical companies.

What of the future?

Other centers are also likely to be admonished. In 1998, Rush-Presbyterian Medical Center in Chicago was given a 5-day suspension. In May 1999, Duke University was issued a letter, suspending its human research. Because Duke was under investigation for only 4 months and responded quickly with a plan to strengthen safeguards of human subjects, the government rescinded their decision only days after the suspension. The institution, however, is required to re-evaluate approximately one tenth of their studies, and the Office for Protection from Research Risk has placed a restriction on the medical center, requiring training and education for research personnel on human subject protection guidelines.

Undersecretary Kiser has established an Office for Research Compliance and Assurance within the Veterans Administration. This office will provide evidence that research is conducted in accordance to safety regulations and with ethical and scientific integrity.

News and Features

Bills may extend working women's rights to breast-feed

see also p. 62

Scott Gottlieb, New York

A woman's right to breast-feed in the workplace is the subject of 3 legislative bills recently introduced to the US House of Representatives. Taken together, the bills aim to extend civil rights protections to nursing mothers and encourage employers to offer special benefits to foster breastfeeding. At least 1 of the bills has wide bipartisan support and appears likely to pass the House later this year, according to a legislative aide to the bill's chief congressional sponsor, Congresswoman Carolyn Maloney (D-NY).

Several political and medical developments over the past few years have prompted companies to adopt policies on breastfeeding at work, mirroring the legislative efforts to guarantee those benefits. In the past 2 years, more than one third of the states have enacted legislation concerning breastfeeding. Most of the new laws, including one in California, concern a woman's right to breast-feed in public. Last year Minnesota required employers to make "reasonable efforts" to provide unpaid break time and a room other than a restroom stall where nursing employees can express their milk in privacy.

Federal legislation introduced by Representative Maloney, called the Pregnancy Discrimination Act Amendment of 1999, would clarify the Pregnancy Discrimination Act of 1978 to protect a woman's right to breast-feed or express milk during the work day. Another provision included in a second and separate bill introduced by Maloney, titled Breastfeeding Promotion and Employers' Tax Incentive Act of 1999, would provide a tax credit for half of the expenses incurred by employers who provide an appropriate environment on business premises for employed mothers to breast-feed or express milk. A third bill—the Right to Breast-Feed Act, which has congressional support from both Republicans and Democrats and appears to be the most likely to pass this year—would guarantee a woman's right to breast-feed her child anywhere on federal property, including public spaces.

"Many women who have contacted my office on this issue have been fired or discriminated against for expressing milk during the day," said Representative Maloney. "Some have been harassed on the job or had their pay docked because they used their regular breaks or lunchtime to pump milk. Some have purchased breast pumps that were painful, ineffective, or damaging."

AP Photo/Lorie Balukoff

Women listening to testimony before the House Law and Justice Committee in Washington on a bill that says breast-feeding in public cannot be considered indecent exposure.

The issue has gained prominence in political circles because of the increasing number of mothers who now work outside the home. In 1960 just 13% of married women with preschool children were employed. Today the number has risen fivefold to 60%, and new mothers are the fastest-growing segment of the labor force.

Increasing pressure has prompted many state governments to consider enacting their own laws in advance of the federal legislation now working its way through Congress. For the third year in a row, the Washington state legislature is being asked to decriminalize breastfeeding in public and require employers to accommodate their breastfeeding workers. The California assembly is considering legislation (Bill #157) that would give women the specific right to breast-feed wherever they are otherwise entitled to be.

Medical experts have pointed to the fact that the United States has one of the lowest breastfeeding rates of any industrialized nation. They cite this statistic as evidence that federal and state governments are not acting fast enough to promote breastfeeding for working mothers. Representative Maloney pointed out that more than three fourths of the countries in the world, but not the United States, conform to the standards set forth by the International Labour Organization (ILO), a United Nations agency that examined the issue. The ILO's standards for maternity include 12 weeks of leave and breastfeeding breaks thereafter totaling at least 1 hour per day. A report released last year found that special breaks for nursing mothers are established law in more than 80 countries, with about half of these nations requiring additional breaks beyond the normal rest periods. The United States currently has no national laws that guarantee special benefits for nursing mothers.

As a result, according to a recent national report by the American Academy of Pediatrics, 59% of new mothers breast-feed their babies at the time of hospital discharge, but

that proportion slips to 22% in 6 months, mainly because many of the mothers return to work. Meanwhile, the American Academy of Pediatrics recommends breastfeeding for at least the first 12 months after birth. "The widespread assumption in America today is that it is neither possible nor reasonable to combine breastfeeding and employment," said Lawrence M. Gartner, M.D., professor of pediatrics at the University of Chicago Medical School. "But there is no reason a mother can't return to work and continue to provide breast milk for her baby."

In response to medical evidence and political pressure, as well as the realization that maternal benefits help retain employees, companies are beginning to offer lactation programs for new mothers. "Among the things companies are doing is allowing breaks and flexible work hours so that women can pump or breast-feed, providing comfortable and private space for pumping, and renting or purchasing electric breast pumps to shorten the time employees need to express their milk," said Rachel Mastow, head of child health and maternal issues for the Washington Business Group on Health, a nonprofit organization that promotes health policy and work-site issues.

"From a corporate perspective, one of the things working in favor of lactation programs is that companies are realizing that it makes economic sense to offer these programs," said Rona Cohen, president of Corporate Lactation Programs for MCH Services, Inc., a company that assists large corporations in setting up maternal lactation programs. "We looked at this and found that it actually ends up saving companies money because it reduces employee absenteeism and promotes healthy babies. The mothers end up missing fewer days from work."

Even when lactation programs have been voluntarily implemented by corporations, says Cohen, "It's still not being offered as an equal benefit to all employees. It's not supported among blue-collar workers."

Survey reveals deficits in women's health care

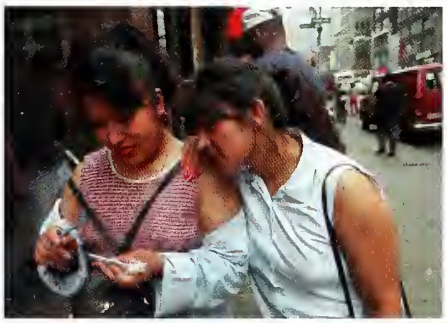
Janice Hopkins Tanne, New York

A study of women's health in the United States by the Commonwealth Fund, a philanthropic organization, has indicated worsening health care and widespread violence and abuse for poorer women. The study, conducted by a national polling organization, was based on telephone interviews between May and November 1998 with 2850 women and 1500 men, chosen as a cross section of the population with an additional over-sample of African-American, Hispanic, and Asian-American women.

Interviewees were asked about health knowledge and behavior, access to care, violence, depression, use of hormone replacement therapy, and caregiving roles. Results published last week showed that since a comparable survey had been done in 1993, the number of noninsured women of working age had increased from 14% to 18%. In the lowest income category—under $16,000 a year—35% of women had no health insurance. The main reason seemed to be a drop in health insurance provided through the woman's job or through her husband's employment.

Only one half to two thirds of the women interviewed had received preventive care in the past year, including a physical examination, clinical breast examination, cervical smear, or cholesterol test, even though 76% of women were in managed care. This number closely matched that of 5 years ago. Women on low incomes and those who did not have a university education were less likely to receive regular preventive care or advice on hormone replacement therapy.

Regardless of insurance coverage, 20% of women under the age of 65 years reported problems in getting the medical care they thought they needed, in gaining access to a specialist, or in getting a prescription filled because of cost.



AP Photo/Kathy Willens

Female workers risk loss of health insurance if they lose their jobs.

The Commonwealth Fund is working with the National Committee for Quality Assurance, an accrediting organization, to identify the health plans that include the best practices in women's health. Senator Patty Murray of Washington has recently introduced a bill in the US Senate that would require managed care plans to cover contraception, mammography, and screening for colon cancer and to provide information about treatments such as hormone replacement therapy.

Violence and abuse were identified as major problems by the survey. Thirty-nine percent of women reported that they had experienced domestic abuse or violence, childhood physical or sexual abuse, or rape. This was the first time the survey asked about these issues, so trends cannot be assessed. The Commonwealth Fund is supporting efforts to train all those who work in healthcare settings, from secretaries and security guards to doctors, to be aware of the signs of violence and abuse and informed about sources of help.

Women were also found to be burdened with the care of sick or disabled relatives, in addition to their jobs and their childrearing responsibilities. Nine percent of women were caring for a relative, compared with only 4% of men, and 43% of women caring for relatives spent 20 hours a week or more on these tasks.

Health concerns across a woman's lifespan: the Commonwealth Fund 1998 Survey of Women's Health is publication number 332 of the Commonwealth Fund Commission on Women's Health. It is available free from the Commonwealth Fund, 1 East 75th Street, New York, NY 10021. It is also posted on the Fund's website: www.cmwf.org

Carvedilol seems no better than metoprolol in treating heart failure

Scott Gottlieb, New York

The newest drug on the market for treating congestive heart failure is no more effective than older beta blockers that cost only a third as much, a study has found (Circulation 1999;99:2645-2651).

Forty-six men and 21 women, aged 29 to 97, with symptomatic stable heart failure were randomly allocated to treatment with either carvedilol, the newest beta blocker, which was approved for use by the US Food and Drug Administration in 1997, or metoprolol, which has been on the market since 1978 and is now distributed in generic form.

After 6 months, researchers found that the two drugs had similar results in increasing stamina, improving the heart's pumping ability, and boosting levels of antioxidants.

The dosages of metoprolol used in the study would cost patients about $23 per month. Comparable treatment with carvedilol costs at least 3 times as much. The study, led by Dr. Marrick L. Kukin, director of the heart failure program at Mount Sinai Medical Center in New York, was paid for in part by pharmaceutical manufacturer SmithKline Beecham of Philadelphia, which makes carvedilol. Carvedilol is also known by the proprietary name Coreg.

Although it is known that the second-generation compound metoprolol is β_1-selective and the third-generation compound carvedilol is β-nonselective, with ancillary pharmacological properties such as a blockade and antioxidant effects, until now it had not been firmly established whether the newer agent offered benefits over the earlier formulation.

Dr. Neil Shusterman, a cardiologist at SmithKline Beecham, which spent $79,000 on the study, said that the findings had been a surprise to the company, because previous research had shown carvedilol to be more effective than metoprolol in improving heart and kidney function and reducing enlargement of the heart.

He said that the new study did not look at some of these factors, and a longer-term study involving large numbers of patients might be necessary.

Center for Organ Recovery and Education, Pennsylvania

A special place—a picture of a garden set up by the federally funded Center for Organ Recovery and Education

Pennsylvania plans to reward organ donation

Fred Charatan, Florida

Pennsylvania is planning to be the first state to offer a financial reward for organ donation. Under a plan being worked out by an advisory panel, the state will pay a stipend of about $300 toward the funeral expenses of an organ donor.

The panel will issue its recommendations next month, and Republican Governor Tom Ridge is expected to approve the new program. Payments authorized by Pennsylvania's Act 102 of 1994 will be made directly to funeral homes, rather than to the family of the organ donor, to avoid violating the federal National Organ Transplant Act of 1984, which classifies human organs as a national resource and bars their sale.

Howard Nathan, who serves on the governor's advisory panel and is president of the Gift of Life Program, 1 of 2 regional networks that distributes donated organs in Pennsylvania, said, "This is absolutely not buying or selling organs. This is about [providing] a voluntary death benefit for a family who gave a gift. The intent is to test it and see if it makes a difference to families."

The stipends will be paid from an organ donor trust fund, which currently has funds totaling $800,000. The payment program will be monitored for 3 years by a panel of medical ethicists to see whether it increases the number of organs that are donated.

According to the US Department of Health and Human Services, 56,716 people were waiting for hearts, lungs, livers, pancreases, and kidneys at the end of 1997. By the end of 1998, the list had grown to 64,423.

Medicine and Money

Why children's health is threatened by federal immigration policies

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Introduction

In response to the growing problem of children's lack of health insurance, the United States Congress, in 1997, appropriated $24 billion to fund state expansions of children's health insurance under the Children's Health Insurance Program (CHIP).[1] Under this program, states can expand Medicaid coverage, establish a separate health insurance program, or use a combination of both programs for children. Children from immigrant families make up a sizeable portion of those eligible for CHIP and Medicaid because they live in families with lower incomes and are more likely to be uninsured.[2,3] According to the General Accounting Office (GAO), 36% of uninsured children who are eligible for Medicaid are from immigrant families, and most of these children are citizens.[4] Immigrants are frightened that using public health insurance could jeopardize their families' immigration status, and this fear may be a major cause of low enrollment of children from immigrant families in Medicaid and CHIP programs. In this article, we discuss recent government actions and contradictory policies that contribute to these fears and explain a new health policy statement by the government to address these fears.

Recent government actions

The US Immigration and Naturalization Service (INS), the State Department, and several state departments of health recently took illegal actions against immigrants. In 1997 and 1998, various state health departments shared confidential information about immigrants' lawful receipt of Medicaid benefits with the Immigration and Naturalization Service and with State Department officials in embassies and consulates through a federal program called the Public Charge Lookout System.[5] No new laws or regulations were issued to authorize such actions. Furthermore, through 2 Medicaid fraud detection programs, the California State Department of Health shared information about immigrants' use of Medi-Cal (California's Medicaid program) from 1994 to 1999 with the Immigration and Naturalization Service.[6] In thousands of cases, officials from these programs warned immigrants that "public charge" determinations would be made based solely on their receipt of Medicaid unless benefits were repaid.[6]

"Public charge" is a term used by the Immigration and Naturalization Service and State Department when referring to immigrants who are likely to become dependent on government benefits in the future.[7] A public charge determination can bar immigrants from becoming legal permanent residents or from returning to the United States after foreign travel; it can limit the ability of immigrants' relatives to immigrate to the United States; and, under limited circumstances, it can result in deportation. Until recently, it was not clear whether the use of Medicaid or other public health insurance should be taken into account in the determination of public charge.

Reports from a variety of sources, including an investigation by the California state auditor and reports from legal advocacy groups and the media, indicate that unauthorized activities of the Public Charge Lookout System and the Medi-Cal fraud detection programs led to unnecessary hardship for many immigrants.[5,8,9] For example, legal permanent residents who had been out of the country for more than 6 months were told by the Immigration and Naturalization Service or by State Department officials that they could not reenter the US until Medicaid benefits they or their children had legally received were paid back.[5] In other cases, US citizens' applications for sponsorship of family members to immigrate were denied until Medicaid benefits were paid back.[9] The Immigration and Naturalization Service, State Department personnel, and state health department investigators told immigrants that receipt of Medicaid would hinder their efforts to become legal permanent residents or obtain citizenship.[5,6] California's State Department of Health Services also sent out letters to immigrants who had lawfully received Medi-Cal, demanding that they repay benefits.[6]

In December 1997, the Immigration and Naturalization Service and the State Department ordered a halt to efforts to collect reimbursements from immigrants who had lawfully received Medicaid. The Public Charge Lookout System was terminated shortly thereafter.[5] Subsequently, Florida decided to give back approximately $200,000 coerced from immigrants by

Summary points

- Citizen children from immigrant families make up a large proportion of those who are eligible for the new publicly funded Children's Health Insurance Program (CHIP).
- Enrollment of immigrants in Medicaid has sharply declined recently, perhaps in part because of their fears that use of publicly funded health insurance could jeopardize their families' immigration status.
- Immigrants' fears may be exacerbated by the fact that recently several federal and state programs unlawfully demanded repayment of Medicaid benefits by thousands of immigrants who were lawfully entitled to receive them.
- The Immigration and Naturalization Service and the State Department should issue a statement clarifying that use of publicly funded health insurance such as Medicaid and CHIP programs will not harm a family's immigration status.
- The Clinton administration recently issued a statement clarifying that use of publicly funded health insurance such as Medicaid and CHIP programs will no longer harm a family's immigration status. Health care providers can play an important role in disseminating this information.

immigration judges and US consular officers abroad.[10] In California, it took a class action lawsuit to get the State Department of Health to agree to repay approximately 1500 immigrants the $3 million they had been illegally forced to pay.[6,9] In early 1998, the budget committee of the California legislature recommended that the state remove funding from 2 Department of Health Services programs that contributed to this miscarriage of justice against immigrants. The programs were not dismantled until April 1999, when the California state auditor's investigation reported continued abuses and recommended their closure.

AP Photo/Kevork Djansezian

Waiting for a "back to school" giveaway in Los Angeles. Children of immigrants face poverty and lack of health care.

Restricting public benefits

Other governmental actions, though less extreme, have contributed to fear and confusion regarding eligibility of children from immigrant families for health insurance. In the past 5 years, several laws aiming to restrict public benefits to immigrants were introduced; the most significant of these, the 1996 Welfare Reform Act, introduced a complex set of new rules governing Medicaid eligibility for children from immigrant families (Table 1).[11] Another law, the Illegal Immigration Reform and Immigrant Responsibility Act of 1996, together with the Welfare Reform Act, mandates that citizenship and immigration status be verified for receipt of federal public benefits. It also mandates that agencies providing 3 types of benefits (Supplemental Security Income, Temporary Assistance to Needy Families [TANF], and federally subsidized housing) must report illegal immigrants to the INS.[11,12]

In California, where nearly 40% of US immigrants live,[3] their fears about enrolling their children in federally funded health insurance may also be influenced by Proposition 187, even though it was ruled unconstitutional and never implemented. Passed by California voters in 1994, Proposition 187 would have denied publicly funded health care, education, and social services to undocumented immigrants, and it would have required providers of these services to report undocumented immigrants to the INS.

Fears of public charge

No published studies in the medical literature have directly investigated the impact of immigrants' fears of public charge on enrollment in Medicaid, but 2 population-based studies provide indirect evidence.[13] Data from Los Angeles County, where 40% of California's uninsured children live,[14] demonstrated a sizeable reduction in applications for Aid for Families with Dependent Children/TANF and Medi-Cal for children between 1996 and 1998.[13] The number of newly approved citizen children of noncitizen parents for these programs dropped by 48%, compared to a 6% increase in citizen children of citizen parents. Noncitizen adults and children approved for Medi-Cal only (not including AFDC/TANF) dropped by 24%, while citizen approvals fell only 7%. A national study, based on the US Census Bureau's current population survey, showed similar results.[15] Between 1994 and 1997, use of Medicaid among noncitizen households fell more sharply (22%) than among citizen households (7%). These drops in immigrant enrollment did not result directly from the Welfare Reform Act's new eligibility rules, because virtually all states retained the eligibility of current immigrants for Medicaid.[16]

Reports of advocacy organizations

Reports in the media and from legal advocacy groups state that the unlawful attempts by the Immigration and Naturalization Service, the State Department, and state departments of health to make immigrants repay Medicaid benefits have had a chilling effect in immigrant communities.[5,8] Several advocacy organizations reported a recent increase in cases of immigrants who refused to enroll in public benefit programs for fear of jeopardizing their families' immigration status.[5] To investigate this problem, the National Health Law Program, the National Immigration Law Center, and a group of state and local advocacy organizations surveyed provider and advocacy organizations across the country in April 1998.[5] The results indicate that fears have led many immigrants to refuse enrollment in government-sponsored health programs and to forfeit both urgent medical care and preventive care. Hospitals reported difficulties obtaining Medicaid reimbursement for emergency services provided to immigrants because of refusals to apply for Medicaid.

Lack of access to medical care can endanger the health of immigrants and others as well. One study showed that patients who feared immigration consequences from visiting a physician were much more likely to delay seeking care for active tuberculosis.[12] In 3 recent rubella outbreaks in New York and North Carolina, the majority of victims

Table 1 *Summary of Medicaid and CHIP program eligibility for immigrants*

Population	Policy
Citizen children of immigrant parents	Medicaid and CHIP programs: eligible
Immigrants arriving before August 22, 1996	
Legal permanent residents	Medicaid and CHIP programs: state option
Asylees, refugees	Medicaid and CHIP programs: eligible for first 7 years of residency; state option afterward
Immigrants arriving on or after August 22, 1996	
Legal permanent residents	Medicaid and CHIP programs: barred for first 5 years of residency*; state option afterward
Asylees, refugees	Medicaid and CHIP programs: eligible for first 7 years of residency; state option afterward
Undocumented or PRUCOL immigrants**	Medicaid: emergency services only CHIP programs: ineligible

*Some states are using state funds to provide Medicaid during the 5-year ban.
**PRUCOL (persons residing under color or law) refers to immigrants legally residing in the United States who do not fit into other immigrant categories.

were unvaccinated Latino immigrants.[18,19] A major obstacle to controlling these outbreaks was that many Latinos feared the health department because they associated it with the Immigration and Naturalization Service.

Nationally, 31% of uninsured children are eligible for Medicaid but not enrolled.[4] When GAO investigators interviewed experts from several states to determine why so many Medicaid-eligible children were not enrolled, they were told that one potential cause was immigrant parents' fears of being deemed a "public charge."[4] Observations from health officials in several states[8,20] and 2 investigations in California support this hypothesis. The California Child Medi-Cal Enrollment Project concluded that the "public charge issue" among immigrant families was one of the top 2 reasons why 38% of the state's uninsured children are Medicaid-eligible but not enrolled (Takeda J, Director, Child Medi-Cal Enrollment Project, written communication, October 27, 1998). Another study using focus groups with parents of Medi-Cal-eligible uninsured children revealed that most Latino parents believed that they would have to repay Medi-Cal benefits received by their children when applying for citizenship.[21]

Immigrants' concerns about the public charge issue could also deter them from enrollment in the new CHIP programs.[22] Results of an investigation by the Medi-Cal Policy Institute suggest that the sluggish rate of enrollment in California's CHIP program, Healthy Families, may be due in part to reluctance among immigrant parents who fear that their children's use of the programs could cause them to be deemed a public charge.[23] In several other states, concern has been expressed that public charge fears could limit immigrant participation in CHIP and other health programs. A few studies have begun to examine this issue.[24-26]

While the studies described above did not directly measure the relationship between immigrants' fears of public charge and their participation in public health insurance programs, they support the conclusions of numerous legal and health advocacy groups. Many immigrants appear not to be enrolling their children because of fears of jeopardizing their families' immigration status. Additional research is needed to measure the extent of this phenomenon and to examine the health consequences of not enrolling children in these programs.

New federal guidelines on public charge

After a year of sustained pressure from public officials, advocacy groups, medical associations, social service agencies, and concerned individuals[8, 27] (National Health Law Program, letter to DeParle NM, July 22, 1998), on May 25, 1999, the Clinton administration issued a policy statement clarifying that use of publicly funded health insurance will not be considered in public charge determinations.[28, 29] The new guidelines clearly delineate for the first time what kinds of benefits may and may not be considered in making a public charge determination. According to this document, public charge determinations will include consideration of 1) receipt of public cash assistance for income maintenance purposes or 2) institutionalization for long-term care at government expense. Benefits that will not be considered in public charge determinations include Medicaid, CHIP programs, nutritional programs, and a variety of other public benefits.

Potential benefits

This long-awaited policy statement is of great potential benefit to uninsured immigrants and their children. Given the government's record of recent abuses described above, however, careful surveillance for improper implementation by overzealous officials is warranted. To allay widespread fears among immigrants regarding use of public health insurance, the new federal guidelines must be unequivocally communicated to all employees of the Immigration and Naturalization Service and the State Department and enforced accordingly. The guidelines also must be publicized widely in immigrant communities. Latino communities should especially be targeted, because over 70% of uninsured Medicaid-eligible children in immigrant families are Latino. By explaining the new federal guidelines to their immigrant patients, healthcare providers and other staff can help to reduce unnecessary fears. Questions on applications to adjust legal status (applications for legal permanent resident status, citi-

zenship, or sponsorship of a relative) should be reframed to ask only about the cash assistance or long-term care programs specified in the new federal guidelines. Currently, applications ask immigrants if they have received any public assistance except emergency Medicaid. Such an open-ended question is likely to cause confusion and increase fears, because immigrants may think that even programs such as the Special Supplemental Nutrition Program for Women, Infants, and Children and school lunch are included.

Over 10 million children in the United States have no health insurance.[2] Unfortunately, contradictory government policies have hindered efforts to address this serious problem. The recent federal guidelines on public charge should begin to remedy this situation; disseminating this information to immigrants who have grown distrustful of government policies will, nevertheless, be challenging. Now that the government has clarified that use of public health insurance will not harm families' immigration status, healthcare providers can assist by explaining this to their patients. Perhaps now Medicaid and the Children's Health Insurance Program can approach their intended goals of providing a needy and eligible population with meaningful access to health care.

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capsule

Smoking in pregnancy can make sons violent A well-crafted Danish study in Archives of General Psychiatry adds to the growing body of evidence linking maternal smoking in pregnancy with antisocial behavior in the offspring (1999; 56:223-224). Data from a cohort of over 4000 men and their mothers show a clear dose-response relation between the number of cigarettes smoked by mothers in pregnancy and their sons' risk of arrest for both violent and nonviolent crime. Mothers who smoked more than 20 cigarettes a day in late pregnancy doubled their sons' risk of arrest for violent crime compared with nonsmoking mothers. Another good reason for young women to quit.

capsule

Pain relief a must for circumcision "No more studies, just do it," goes the subtitle of an Op-Ed urging physicians in the US to give analgesia to newborns during routine circumcision. (Archives of Pediatrics and Adolescent Medicine 1999; 153:444-445). The two authors describe circumcision without pain relief as unconscionable, and blame inadequate training, ignorance of the evidence and a lack of interest for the persisting practice. Nothing will change, they say, until leading medical societies demand their physicians wake up and learn to do dorsal penile nerve blocks.

Speaker's Corner

Breast is best, but...

Let me admit from the outset that I am a breastfeeding zealot. I was not always a zealot. For most of my life and for the first part of my medical career, I was merely a mainstream breastfeeding supporter, one who believed that it was a good idea to support breastfeeding—wonderful if it happened, but okay if it didn't. Then Ian, a 7 lb 4 oz miracle, joined my life, and I began my transformation.

Being a family physician and a woman of the '80s, I had every intention of breastfeeding my baby for at least a year. He was a vigorous breastfeeder from his first effort in the delivery room. Maybe a bit too vigorous those first few weeks, but it soon became enjoyable as well as miraculous.

Then I went back to work.

At the time, I was in a group practice in a small midwestern town. My partners were, like me, mainstream breastfeeding supporters. Our family physician (who was also my practice partner) had breast-fed her children, as had several of the office nurses. I had the perfect working situation for breastfeeding: a private office in which to pump, a refrigerator for storing milk, a caregiver for my child who was nearby so I could visit at lunch time, and a very supportive spouse. No problem, right?

It didn't take long for me to find out that the people around me felt that breast is best, but not if it inconveniences someone, not if it takes precedence over other matters, not if it goes on for more than 6 months.

In all fairness, I never experienced any direct harassment or criticism. What I did experience was episode after episode of lack of real support and repeated misunderstandings. Since going through this experience and ending up a zealot, I have observed others in similar situations. I have come to realize that the health professions are not really as supportive of breastfeeding as they could be.

Let me give you a few examples of what I experienced, and what I have seen others experience. Before I officially returned to work, I went to the office with my new baby to do prenatal checks on some of my maternity patients who were approaching their due dates. I gave explicit instructions that I was only going to see my maternity patients and would not see anyone who was sick because I would be seeing patients with my baby tucked into the front pack with me. Still they put in someone with an upper respiratory infection and a rash because everyone else in the practice had a full schedule, and I was only seeing a few patients.

> There I was, leaking like crazy and needing to get to my baby.

When I did go back to work, I arranged my schedule to start earlier in the mornings so I could have a mid-morning "pump break" and a longer lunch hour to feed my baby. My morning was just as long as everyone else's because I started earlier, but I finished earlier. Because I was the first one to complete my schedule each morning, they would put in a late morning walk-in for me. There I was, leaking like crazy and needing to get to my baby. When I declined to see the patient until after I returned from lunch, I was told I was not being a team player—even though I offered to come right back after nursing rather than take more time to eat.

After a particularly stressful period, I wanted to reduce my working hours to get more rest and allow my milk supply to recover so I could continue nursing exclusively. My doctor/partner replied, "But that's what formula is for!"

One of my residents sadly weaned her baby before starting her residency because she didn't think she could handle internship and breastfeeding. She may well have been right, but I wish I had been able to help her make some plans in advance.

My office nurse is breastfeeding her second child. She too faces the reproach, "We support you, but not if it inconveniences us or the patients." She struggles to find time

to pump and to get out of the office for her nursing/lunch breaks.

So what's the problem? Is breastfeeding just a "nice touch," important for 6 weeks or so, but not so important later? Clearly, breastfeeding matters. The recent American Academy of Pediatrics policy statement[1] outlines the many risks of not breastfeeding, including risks to otherwise healthy babies.

It is striking that breastfeeding education in medical and nursing schools is woefully inadequate. Resident physicians, even in specialties that claim to support breastfeeding, have especially challenging experiences when they try to breast-feed. Physicians (and nurses, I presume) tend to give breastfeeding advice based on their own breastfeeding experiences, good or bad. This makes it absolutely critical that we educate health professionals about breastfeeding and do everything we can to ensure that female health professionals and the spouses and partners of male health professionals have positive breastfeeding experiences. They can convey real support to each other and to their patients during the breastfeeding phase of child rearing.[2] This is the only way we will be able to change our culture's view from "Breast is best, but ..." to, simply, "Breast is best."

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Doctor, test thyself

While a fourth-year medical student, I developed blurry vision. I was told by neurologists that I needed a magnetic resonance imaging (MRI) of my head. No one told me how this test was performed until I got to the MRI suite. I was informed that I needed to lie still for 45 minutes in a circular tube where I would periodically hear some loud noises.

As I lay there in a humiliating gown that exposed my posterior, with my skin against the stone-cold surface of the table, I was glided into a circular enclosure, and a metal muzzle-like grid was placed over my head to prevent me from moving during the test. I was told not to move, not to speak, not to even blink my eyes if I could help it. I heard machine gun–like noises for 5 to 10 minutes at a time. I could only wonder why I wasn't carefully prepared for this test. Did my doctor even know what he was putting me through?

Seven years later, after I completed medical school, residency training, and a fellowship, my wife had to undergo a barium enema. She asked me what would happen. Clearly, her physician had told her nothing. No problem. She had me for a husband. This was a test I ordered all the time. I told her that they would put some barium in her rectum and take sequential X rays to visualize her colon.

She came home that night and could barely look me in the eyes. I asked her how the test went. She described stripping down below her waist and being strapped face down to a stone-cold table. She had to spread her legs so a tube could go into her rectum to allow barium dye to be forcefully and painfully injected into her colon. As the dye was injected, they turned her upside down and swayed her back and forth to help the dye disperse through her colon. I was mortified.

Why didn't her doctor prepare her for this test? Why didn't I know what this test involved? How often have I ordered this test without fully explaining the procedure to my patients? Shame on me. I thought about how many other tests I order with no idea what I'm putting my patients through: esophograms, myelograms, carotid duplex scans, angiograms, venograms, fluoroscopic-guided biopsies—the list goes on and on. I had an excellent training in when and why to order all these tests, but was never taught to see them through patients' eyes. Is our training so information-oriented and coldhearted? How many other doctors order tests in the same insensitive way that I have been ordering them? Shame on all of us. Most of us have not seen the procedures required by many of the tests that we routinely order. The ones that we can best explain to our patients are the ones that we have been through ourselves.

To prevent this from happening to our medical students, we created a curriculum that gives students the opportunity to watch many of the tests and procedures that we order. We ask our students to observe at least 2 tests or procedures for 1 of the organ systems they learn about during their second-year Fundamentals of Clinical Medicine (physical exam) course, then report back their experiences to their small clinical skills groups.

Although it is important for medical students to understand the details of each particular test, the main goal is to help them grasp the physical and emotional trauma that can be associated with some of these diagnostic tests and procedures that they will be ordering as physicians.

The program is very successful. We hope that this exercise will continue to create physicians who are more understanding of what patients go through to obtain quality medical care. Clearly, this type of exercise needs to be continued not only in the third and fourth years of medical school but also during residency training.

By the way, I don't order barium enemas anymore.

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Specials thanks to Michael Wilkes and Bill Heath for their encouragement and support for this program, and to my wife, Debby, for opening my eyes to some of the pains of patient care.

Letter from the Northwest

Chronic pain—what a pain

John Roberts, Madrona Medical Group, Northwest Campus, Bellingham WA 98225, jcroberts@hinet.org

Early in medical school, we learned that pain is the core of the medical interview—location, characterization, radiation, associations, and timing. We learned that pain is legitimate or it is not. It is legitimate when we can find an objective cause, such as cancer. It is illegitimate if we cannot place a causal label on it. Instead of accepting that most pain is caused by syndromes whose mechanisms we doctors fail to comprehend, we sometimes blame the patients, calling them "drug seekers."

What we did not learn was how to treat most pain. Once we entered practice, it became clear that chronic pain without an obvious source is one of the most common reasons people visit doctors. Upwards of 30% of Americans say they have chronic pain.[1, 2] These people use medical resources more often than others. The average primary care doctor will see 8 to 10 patients a week for chronic pain. These people seek out other sources for pain relief as well. Chronic pain doubles the chance that a patient will seek out alternative healers.[3]

Chronic pain is costly. Chronic pain patients tend to be poorer than other patients, but it is not clear whether poverty is a cause and or an effect.[4] A last resort of primary care physicians is usually a multidisciplinary pain clinic. Only about 200 such centers exist in the United States. Their average cost is about $8,100 per patient, and many insurers will not pay the bills. But they will pay the $18,000 a year the average pain patient spends as he searches futilely for relief.[5]

Chronic pain is dangerous. For some, it is terminal. About half of sufferers report that they have seriously considered suicide.[6] Chronic pain raises the risk that a suicide attempt will be successful.[7] Pain sufferers have a greater incidence of psychiatric diseases: as many as two-thirds suffer clinical depression.[8] But again, we should wonder if depression is a cause or a result of chronic pain syndromes.

So if pain is common and life-threatening, why aren't we doing more to relieve it ? Why do we hand patients some anti-inflammatory drugs and maybe some antidepressants and then send them on their way, perhaps even secretly hoping that they will be among those 20% who frequently switch doctors?[6]

First, we're not set up to handle chronic pain. It is a long-term syndrome that demands lengthy time with a patient. Primary care visits run 15 minutes. The doctor sits on a rolling stool, which seems to roll rapidly toward the conclusion of the visit. The patient is perched high up on an exam table, sometimes in a paper gown. This scene does not promote a thoughtful answer to such questions as "What does pain mean for you in your life?" or "Can you imagine what your life would be without pain?" These are the sorts of questions that help patients begin to understand their own pain. They create an opening for the patient to be more active in finding relief.

Second, we tire of drug seekers. Every practicing doctor has encountered the drug seeker who presents himself as a patient with chronic pain. Many knowingly seek opioids and benzodiazepines, but some remain unconscious of their behavior. Perhaps we are no more conscious. Sometimes I will recognize such patients because of narcotic creep, their tendency to want just a little more each month. The drug-seeking diagnosis is made more firmly by a pharmacist who calls to tell me that my patient is getting opioids from half a dozen other doctors.

We need to consider our attitudes toward opioids. They work. They relieve pain. They don't cure the underlying illness—but then we can't find an underlying illness to cure. The experts who sit in criticism say that we practitioners fear we will create addicts. I doubt their hypothesis. My own hesitancy to prescribe comes from our country's war on drugs and my fear that I'll become labeled a drug dealer if I become more liberal in my prescribing behavior.

Such fears are warranted. I have a patient with chronic abdominal pain, probably due to an occult gastrinoma as part of her multiple endocrine neoplasia. She has gone through virtually every long-acting opioid and has found relief only with 6 tablets of oxycodone every 2 hours—360 mg a day. A few months ago I got a call from a state health inspector. She asked me rudely, "Do you know what you're doing, Doctor?" She accused me of incompetency and demanded that I send my patient to a pain specialist. (She had already seen 3.)

But even the pain specialists can be threatened. A psychiatrist and colleague of mine who sees chronic pain patients several times each day has had excellent results with his careful but somewhat liberal use of opioids along with exercise and behavioral therapy. He was reported by another doctor for overprescribing narcotics. He spent great amounts of time and money on a lawyer and additional hours of his own time testifying before regulators. Judgment was not swift. He recently got the verdict in a brief letter: not guilty—6 years after the investigation of his behavior began.

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NOVEMBER 5-7, 1999: 11th Annual Anesthesiology Update. Monterey Plaza, Monterey, CA. Contact (916) 734-5390.

NOVEMBER 4-6, 1999: UC Otolaryngology Update: 1999. UCSF at Ritz-Carlton Hotel, San Francisco, CA. 18.5 Cat I hrs. $425. Contact (415) 476-5808.

CARDIOLOGY

JULY 25-29, 1999: Nineteenth Annual Current Concepts in Primary Care Cardiology. UC Davis School of Medicine, Division of Cardiovascular Medicine. Granlibakken Conference Center, Tahoe City, CA. Contact: Kimber Chavez, Program Representative at (916) 734-1394 or kimber.chavez@ucdmc.ucdavis.edu.

OCTOBER 7-9, 1999: 23rd Annual Cardiology Update 1999. American College of Cardiology at Carmel Valley Ranch Resort, Carmel, CA. 12 Cat. I hrs. Contact: Registration Secretary, Extramural Program Dept., American College of Cardiology, tel (800) 253-4636, ext. 695, fax (301) 897-9745.

OCTOBER 13-17, 1999: Coronary Interventions 1999. Scripps Clinic at Hilton La Jolla Torrey Pines, San Diego. Contact: Jill Hofmans, Conference Services Supervisor, Scripps Clinic. Dept. of Academic Affairs, 403C. 10666 N. Torrey Pines Rd., La Jolla, CA 92037; tel (619) 554-8556; fax (619) 554-6310.

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JULY 30-AUG 1, 1999: Coronary Heart Disease Update. Medical Education Resources at Tenaya Lodge, Yosemite, CA. 11 hrs. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Ct., Ste. 500, Littleton, CO 80120-4569; (800) 421-3756.

AUGUST 6-8, 1999: Managing Respiratory Diseases. Medical Education Resources at the Hyatt Regency Monterey, CA. 11 hrs. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Ct., Ste. 500, Littleton, CO 80120-4569; (800) 421-3756.

AUGUST 20-22, 1999: Primary Care Medicine. Scripps Clinic at Coronaro Island Marriott Resort, San Diego. 16 hours. Contact: Cheryl Trinidad, conference Coordinator, Scripps Clinic, Dept. of Academic Affairs, 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037; tel (619) 554-8556; fax (619) 554-6310.

OCTOBER 2-4, 1999: 7th Annual Western Retreat: Practical Primary Care. Scripps Clinic at Monterey Marriott. 12 hours. Contact: Cheryl Trinidad, conference Coordinator, Scripps Clinic, Dept. of Academic Affairs, 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037; tel (619) 554-8556; fax (619) 554-6310.

OCTOBER 22-24, 1999: Clinical Endocrinology for Primary Care Physicians. Medical Education Resources at the Tropicana Hotel in Las Vegas, NV. 11 hours. Contact: MER Linda Main, Meeting Coordinator, 1500 West Canal Ct., Ste. 500, Littleton, CO 80120-4569; (800) 421-3756.

OCTOBER 28-31, 1999: 11th Annual CME/Golf Meeting. Nevada Academy of Family Physicians at The Orleans Hotel & Casino, Las Vegas, NV. Contact: Barbara Bolling, NAFP, P.O. Box 27713, Las Vegas, NV 89126-1713. (702) 228-5852; nafplvbb@aol.com

INTERNAL MEDICINE

AUGUST 22-27, 1999: New Advances in Internal Medicine. UC Davis at Embassy Suites, Monterey, CA. Contact UCD (916) 734-5390.

OB/GYN

SEPTEMBER 25-26, 1999: Ultrasound Update: 1999. Hilton Hotel, Sacramento, CA. (916) 734-5390.

DECEMBER 10-12, 1999: Issues in Women's Health. Tropicana, Las Vegas, NV. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; tel (800) 421-3756; fax (303)798-5731.

OCCUPATIONAL & ENVIRONMENTAL

AUGUST 5-6, 1999: Occupational & Environmental Toxicology for the Health & Safety Professional. UC Berkeley. Holiday Inn Bay Bridge, Emeryville, CA. Contact: Center for Occupational & Environmental Health, UC Berkeley, Richmond Field Station, 1301 S. 46th St., Bldg. 102, Richmond CA 94804; (510) 231-5645; http://socrates.berkeley.edu/~coehce/.

SEPTEMBER 23-26, 1999: Western Occupational Health Conference (WOHC). American College of Occupational and Environmental Medicine and the Western Occupational and Environmental Medical Association at Monte Carlo Resort and Casino, Las Vegas, NV. 21 hours. Contact: Justine Abel, WOHC, 74 New Montgomery, Suite 230, San Francisco, CA 94105-3411; tel (415) 764-4083; fax (415) 764-4915; woema@hp-assoc.com; www.woema.com.

ONCOLOGY

SEPTEMBER 17-18, 1999: 5th Annual Cancer Research Symposium. UC Davis at Cancer Center Auditorium, Sacramento, CA. Contact: Office of CME, UC Davis Medical Center, 2315 Stockton Blvd., Camellia Cottage, Room 1019, Sacramento, CA 95817; tel (916) 734-5390; fax (916) 734-8966.

OCTOBER 14-16, 1999: 23rd Annual Physicians Cancer Symposium. Scripps Health, Stevens Cancer Center, San Diego, CA at La Jolla Hyatt Regency Hotel. 16.5 CME hours. Contact: Ruthanne Crawford, Stevens Cancer Center, Scripps Memorial Hospital 9888 Genesee Avenue, La Jolla, CA 92037; tel (619) 626-6756; fax (619) 626-6793; racrawford@ch2.edu.

OCTOBER 14-16, 1999: 19th Annual Nurses Cancer Symposium. Scripps Health, Stevens Cancer Center, San Diego, CA at La Jolla Hyatt Regency Hotel. 18 contact hours. Contact: Ruthanne Crawford, Stevens Cancer Center, Scripps Memorial Hospital 9888 Genesee Avenue, La Jolla, CA 92037; tel (619) 626-6756; fax (619) 626-6793; racrawford@ch2.edu.

PEDIATRICS

JULY 16-17,1999: Seventh Annual Pediatric Update. Sponsored by Lucile Packard Children's Health Services at Stanford and faculty from UCSF and Stanford Schools of Medicine. Lucile Packard Children's Hospital. Contact: Elinor Meyer, Continuing Medical Education and Physician Relations Department, Lucile Packard Children's Hospital, 725 Welch Road, Palo Alto,CA 94304; (650) 497-8554.

PRIMARY CARE

JULY 25-29, 1999: 19th Annual Current Concepts in Primary Care Cardiology. Granlibakken Conference Center, Tahoe City, CA. (916) 734-5390.

OCTOBER 22-24, 1999. Clinical Endocrinology for Primary Care Physicians. Tropicana, Las Vegas, NV. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; tel (800) 421-3756; fax (303) 798-5731.

RADIOLOGY

SEPTEMBER 25-26, 1999: Ultrasound Update: 1999. UC Davis at Hilton Hotel, Sacramento, CA. Contact: UCD (916) 734-5390.

RESPIRATORY

AUGUST 6-8, 1999: Managing Respiratory Disease. Monterey, CA. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; tel (800) 421-3756; fax (303)798-5731.

GENERAL/MULTIDISCIPLINARY

AUGUST 24-25, 1999: BLS Instructor Course. American Heart Association at San Leandro. 11 hrs. Contact: CPR Seminars (925) 754-7900.

OCTOBER 15-17, 1999: Physician Leadership Program. California Academy of Family Physicians at Laurel Heights Conference Center, SF. 20 hrs. $1245-$1395. Contact: Laura Johnson Morasch (415) 394-9121. Web: www.familydocs.org/ Orgs?hcli.html (e-mail: HCLI@familydocs.org).

GENERAL

OCTOBER 1-4, 1999: Converse in Spanish. Maricopa Health System at Scripps Memorial, San Diego. 36 hrs. $695. Contact: Rios Associates (619) 218-4875.

OCTOBER 21-25, 1999: Masters of Medicine 1999. Continuing Medical Education Associates at Maui Marriott, Maui HI. 30 hours. $795. Contact: CMEA, PO Box 57072, Irvine, CA 92619-7072. Tel (800) 447-4474 or (949) 250-1008; fax (949) 250-0445.

ACLS Provider/renewal. June 22-23, July 10-11, September 23, October 11-12, November 9, 1999. $115. For details: CPR Seminars at (925) 754-7900.

LOSS PREVENTION

SEPTEMBER 22-25, 1999: Legal Issues in Damaged Brain Injury Cases. Westin St. Francis Hotel, San Francisco, CA. Contact (916) 734-5390.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, P.O. Box 7690, San Francisco 94120-7690. (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. CD ROM. $70. 2 hrs. Contact: Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850. Brochures, course information, and registration forms are available from the contact person or organization.

TUESDAY NOON CONFERENCES: Various Topics in Medicine. Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

FIRST WEDNESDAY OF EACH MONTH: Various Topics in Neurology. Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

SECOND WEDNESDAY OF EACH MONTH: Cardiovascular Education Series. St. Anthony Hospital at St. Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo Contact—University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; fax (303) 372-9065.

IDAHO

To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930. Brochures, course information, and registration forms are available from the contact person or organization.

JUNE 10-12, 1999: 22nd Annual Snake River Medical Forum. St. Joseph Regional Medical Center at Red Lion Hotel, Lewiston, ID. Contact: Koleen Wagner at (208) 799-5460.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

EVERY FIRST AND THIRD TUESDAY: Building and Implementing Clinical Practice Guidelines at the Point of Care. Contact: Thomas A. Naegele, DO, (505) 275-7267.

JULY 30-AUGUST 1, 1999: Neurology for the Non-Neurologist. Eldorado Hotel, Sante Fe, NM. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; (800) 421-3756; fax (303)798-5731.

AUGUST 14, 1999: Tenth Annual Update in Primary Care. New Mexico Hispanic Medical Association at the Crowne Plaza Hotel, Albuquerque, NM. Contact: Kelly Little at (505) 828-0237; fax (505-828-0336.

OCTOBER 7-9, 1999: Santa Fe Colloquium on Cardiovascular Therapy: Can Coronary Artery Disease be Stabilized or Reversed? What About Primary Prevention? American College of Cardiology at Eldorado Hotel, Santa Fe, NM. 17 Cat I hrs. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology; (800) 253-4636, ext. 695; fax (301) 897-9745.

Satellite Courses
Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366.

CONTACT INFORMATION
UNMSOM: University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

All courses listed meet the criteria for Category 1 of the Physician's Recognition Award of the AMA. To list AMA Category 1 CME courses, send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address. NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

WEEKLY: Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics. Contact: UUSM.

WEEKLY: Pediatric Grand Rounds. Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA98121; or phone (206) 441-9762 or (800) 552-0612.
Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION
CME HARBORVIEW: Contact–Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA98104. (206) 223-5953. PCMS CME Contact—Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137. U/W (UNIVERSITY OF WASHINGTON) Contact—U/W School of Medicine, Div. of CME, SC-50, Seattle, WA98195. (206) 543-1050. VMMC (VIRGINIA MASON MEDICAL CENTER) Contact—Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, POBox 900, Seattle, WA 98111. (206) 340-2058. WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

All courses meet the criteria for Category 1 of the Physician's Recognition Award of the AMA. To list AMA Caegory 1 CME courses here, send information at least two months in advance to the Medical Education Committee, Wyoming Medical Society, P.O. B ox 4009, Cheyenne, WY 82009; email skeefe@wyomed.org; tel 307 634-2424; fax 307 632-1973.

AUGUST 30-SEPTEMBER 1, 1999: Tutorial in the Tetons. American College of Cardiology at Jackson Lake Lodge, Moran WY. 14.5 CME. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699; tel (800) 253-4636, ext. 695; fax (301) 897-9745.

JULY 20-23, 1999: Occupational and Environmental Medicine in Primary Care. Rocky Mountain Center for Occupational and Environmental Health at Jackson Hole, WY. Contact: Registration Coordinator, The Rocky Mountain Center for Occupational and Environmental Health, (801) 581-5710.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

JULY 18-21, 1999: Eighth National Alzheimer's Disease Education Conference. Alzheimer's Disease and Related Disorders Association at Long Beach Convention Center, Long Beach, CA. Contact: Nicolle Heller, Alzheimer's Association, (312) 335-4037; Nicolle.Heller@alz.org.

SEPTEMBER 30-OCTOBER 2, 1999: 7th Annual Conference on Management of the Tinnitus Patient. University of Iowa College of Medicine at Medical Alumni Auditorium, Room E331 UIHC, The University of Iowa Hospitals and Clinics, Iowa City, IA. Contact: Cheryl Schlote, Phone: (319) 384-9757; fax (319) 353-6739; cheryl-schlote@uiowa.edu.

Guidelines for Authors

Our readers represent all disciplines of medicine, but principally primary care physicians. We aim to publish manuscripts that are reliable and lively and that will improve the care of patients, the health of the public, or policies affecting either. Manuscripts should be of interest to a broad range of busy practitioners, physicians in training, and anyone who has an interest in quality health care. The purpose of a paper or letter may be to report, inform, alert, review, and discuss, but, above all, to teach. We aim to give quick and informative decisions on the articles we receive.

Manuscript submission information

Manuscripts should be sent to:
Managing Editor, Catherine Nancarrow,
WJM Western Journal of Medicine,
221 Main Street, PO Box 7690,
San Francisco, CA 94120-7690;
wjmsf@pacbell.net.

Manuscripts may be submitted via e-mail, but must include print mail address and phone and fax numbers of the correspondent.

Manuscripts must be original, not previously published, and not under consideration by another publisher. If preliminary data were included in another presentation or publication, this should be noted in the cover letter and a copy of that publication should be included.

Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal). Research or project support should be included as a footnote to the manuscript and detailed in the Letter of Transmittal. Obtaining informed consent to protect patients' rights to privacy should be documented according to URM 1997.

All manuscripts should be double-spaced and, including references and abstract but not tables, should not exceed:

- **Original articles**: 2,500 words with a maximum of five tables and 30 references; structured abstract
- **Topics in Review**: 1,500 to 2,000 words with a maximum of 25 references; summary points†
- **Topics for Best Practice:** 2,000 words
- **Evidence-Based Case Reviews:** 2,500 words with two tables and/or figures; summary points†
- **Commentaries:** 600-800 words
- **Letters to the Editor:** 500 words

Structured abstracts

Manuscripts, except for case-based reviews, should include a structured abstract of no more than 250 words with the headings: objectives, design, setting, subjects, interventions, main outcome measures, results and conclusions.

Evidence-based case reviews

Interesting cases presented in an evidence-based, case-based review format provide readers with information and guidance with respect to clinically relevant choices made by practitioners—from diagnostic methods to conclusions as to what might have been done differently given the outcome. Topics to address include:

- epidemiology
- differences in demographic groups
- an evidence-based approach to diagnosis, management, and therapeutics; ethical issues
- cost/economic issues; when to involve a specialist
- what research is needed in the area.

Use of diagrams, tables, and algorithms is highly recommended. Authors should include 5-7 bulleted summary points for a busy primary care provider.

Letters to the editor

Letters must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review.

Letter of transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone and fax numbers included.

A letter of transmittal, except for one accompanying a manuscript from US government employees whose work was done as part of their official duties, must include:

- a paragraph that **transfers copyright:** "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to *WJM Western Journal of Medicine,* in the event that such work is published by the journal."
- a statement of **author responsibility** signed by all authors: "I have participated in the conception and design of this work and in the writing of the manuscript and take public responsibility for it. I have reviewed the final version of the

manuscript and approve it for publication. I attest to the validity and legitimacy of data in the manuscript and agree to be named as the lead author or coauthor of the manuscript."

- a description of **sources of funding and the role of sponsors,** including their involvement, if any, in review and approval of the manuscript for publication.
- a statement of **financial disclosure:** "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed in the attached statement)."
- a statement that all human subjects involved in experimental investigation gave their **informed consent** and that approval was obtained from the appropriate institutional review board.

Editorial review

All manuscripts are subject to peer review in addition to review by the Editors to determine the originality, validity, and importance of content and conclusions. *WJM* aims to introduce an open peer review system; reviewers' comments may be signed. Reviewers are required to state all possible conflicts of interest.

All accepted manuscripts are subject to copyediting. The corresponding author receives edited page proofs for approval and minor changes and is responsible for clearing all corrections and changes with coauthors.

Manuscript preparation

All manuscript materials, including references, tables, figure legends, and abstracts, must be double-spaced.

Please submit the following:

- The original manuscript, two copies, and a copy of the manuscript (including references, tables, and figure legends) on disk (formatted for a PC/Windows platform and labeled with the word processing program used). Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides.
- Figures, black and white or color, in triplicate unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints (and transparencies for color figures) with the figure number, lead author's name, and top of the photo indicated with a label on the back.

WJM encourages the use of illustrations and asks authors to submit photographs for publication. When possible, patients should be asked to sign consent forms before pictures of them are published. This should be clearly stated and proof submitted with the manuscript. If obtaining consent is not possible, the reason should be stated in the cover letter. Changing the data on patients should not be used as a way of securing anonymity.

Figure legends, to be typed in sequence on the same page, should be in complete sentences. A letter of permission to borrow from the copyright holder (the previous publisher) must accompany any figures or tables previously published. The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

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A form for ordering reprints will be sent to the corresponding author when the article is published.

References

All references should be cited in the text using superscript numbers and listed in their order of citation. Reference style should follow guidelines adopted by the US National Library of Medicine. The title of the article, name of publication, year of publication, volume number, and first and last page numbers should follow the authors' names.

Journal articles

Abbreviations of journal titles should conform to those used in Index Medicus. List up to three authors; for four or more, use et al. after listing the first three.

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. *Ann Intern Med* 1996; 124:980-982.

Books

Ringsven MK, Bond D. *Gerontology and Leadership Skills for Nurses.* 2nd ed. Albany (NY): Delmar Publishers; 1996.

Personal communications and unpublished data

The use of "personal communication" or "unpublished data" should be avoided and should not be included in the reference list.

For further information

Questions regarding the Guidelines for Authors may be directed to the Managing Editor in writing at the address above or by telephone 415-974-5977, fax 415-882-3379, or e-mail (wjmsf@pacbell.net).

Author checklist

- Original double-spaced manuscript and two copies, as well as PC-formatted disk.
- Illustrations, glossies and/or transparencies, identified with lead author's name, plus figure legends that describe fully and in complete sentences what the figure depicts.
- Letter of transmittal that includes release of copyright, statement of conflict of interest, funding source(s), and authorship responsibility, signed by all the authors.
- A 250-word structured abstract.
- Title page that includes current affiliation of all authors and all contact details for the corresponding author (street and e-mail addresses, phone numbers, fax numbers).
- Permission-to-borrow letters for any previously published illustrations or tables.
- Informed consent obtained.

A rain ceremony in Uganda

David Heiden

Father Mario Cisternino, a Catholic missionary to the Karamoja tribe, took me with him to a village where he conducted a Sunday mass, attended by a few of the women, a cluster of cows, and a blind man. By chance, the tribe was having their own religious ceremony that day, an "Akiriket," to pray for rain. This was in the summer of 1983, when the drought that would devastate much of Africa was beginning.

We followed the tribe about a mile into the Savannah bush, to a gentle rise in the landscape, where the entire village had assembled. They were organized with a ceremonial protocol as formal as a Catholic mass, and I walked with Father Mario to the half-circle of branches where a cow had been sacrificed and the elders now stood. With Father Mario translating and guiding the exchange we talked, and he told them I was an American.

Yes, they knew of my tribe. One of them pointed up at the sky, and Father Mario nodded his head and translated, "They say you come from the tribe that makes the guns and the airplanes." They asked if my tribe sacrificed animals, and they asked to hear one of our prayers. We moved to the outskirts of the group and their chants began.

Shortly after the ceremony ended, it rained.

David Heiden is an ophthalmologist practicing in San Francisco.

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This month in wjm

Physicians should admit their mistakes

When patients are unintentionally injured during treatment, physicians may avoid telling them because it's difficult, it's unpleasant, and they might get sued. On page 81, a questionnaire survey by Hingorani et al. of over 300 patients at an ophthalmology clinic shows that almost all believed they should be told when complications occurred. Only 60% of the ophthalmologists surveyed agreed. In his commentary on page 82, law professor Henry Greely argues that medicine cannot be free of mistakes and that admitting them to patients and to oneself should be an ethical requirement and a practical prerequisite to minimize future errors. But, he warns, we need a healthcare system that encourages rather than punishes this practice.

Cirrhosis mortality seems linked with consumption of spirits

Mortality from cirrhosis peaked in 1973 in the United States, after climbing steadily since World War II. This peak occurred several years before total per capita consumption of alcohol peaked and began to decline. On page 83, Roizen et al. report that cirrhosis mortality is more strongly associated with spirit consumption than with either total alcohol or just beer and wine consumption. On page 88, Kernochan and Yee argue that spirit consumption may serve as a marker for some societal change. They suggest that total spirit consumption does not take into account that only a small proportion of heavy drinkers consume enough to put them at risk of cirrhosis. Fortunately, as Anand discusses on page 110, hepatology has seen major advances in the past decade, although the only definitive treatment for end-stage liver disease is still transplantation.

Life as a medical specimen

Mark Gash is a 43-year-old painter, actor, and website designer who lives in Hollywood, California. He is also disabled by osteogenesis imperfecta #3. On page 135 he describes, without self-pity, the problems of growing up different. It wasn't only people in stores who pointed at him. Physicians, too, treated him like a specimen. At times, they made him feel like he was a stamp in their collections. Physicians, he pleads, should speak in a way that patients can understand.

Patients with disabilities need help with sexual problems

Disabling conditions can produce problems of desire, arousal, orgasm, or sexual pain in men and women. Patients with an impairment that is hidden from others but that affects continence or sexual function often find the situation humiliating and avoid all social contact. Physicians often forget or are too embarrassed to ask about these issues. On page 107, Glass and Soni discuss conditions that may cause sexual problems and warn that patients can lose self-esteem and become depressed and may, without help, be denied the opportunity to have children. In an Op-Ed on page 76, Huang argues that physicians do not serve their disabled patients well by ignoring such a vital part of their lives.

How to care for patients with developmental disabilities

Patients with developmental disabilities can be frustrating to treat and expensive in terms of time and resources. On page 92, Doostan and Wilkes provide an evidence-based case review of how best to care for such patients. Some of their evidence comes from focus groups of developmentally disabled patients and/or their caretakers, organized with the help of the Lanterman Regional Center in Southern California. The review suggests techniques for caring for people with disabilities and ways of understanding patient and family expectations. It also looks at some of the ethical and management controversies that can arise.

Controversy over mandatory reporting of domestic violence

The US Department of Justice estimates that almost one million women are assaulted by intimate partners every year, and over half of these assaults result in injury. Up to one third of women injured in domestic assaults seek medical care at emergency departments or community clinics. Five states have mandatory reporting laws that specifically address suspected cases of domestic violence injuries: California, Colorado, Kentucky, New Hampshire, and Rhode Island. On page 118, Bauer and Mooney provide background on the laws and suggest a way forward. Larkin and O'Malley argue on page 119 that mandatory reporting improves treatment and identification of the problem, while on page 121, Schillinger and Hyman warn that the law puts women at risk from retaliation and may deter them from seeking help. On page 125, MacGregor explains how mandatory reporting translates into the community and suggests that physicians learn about services available to battered women.

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Op-Ed

Discussing sex with disabled patients

A conspiracy of silence is harmful and unnecessary

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Mattel Children's Hospital
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Health is not only the absence of illness but also overall psychological and physical well-being. An important aspect of this well-being is sexual health. Unfortunately, though, in caring for the chronically ill or disabled, physicians often overlook sexuality. There is no question that physical illness can affect social functioning. The medical literature is full of references to the social impact of illnesses such as cancer or spina bifida. Patients with chronic conditions often list sexuality as a primary concern.[1, 2] Physicians may discuss social behaviors, such as tobacco and alcohol use, but all too often neglect to discuss sexual concerns.

Both patients and physicians may be uncomfortable bringing up sexuality. Patients often prefer that their physicians broach the subject, but for this to happen, physicians must be comfortable discussing sexuality, a topic fraught with controversy and embarrassment. Many studies show that physicians are apprehensive about discussing sexual issues with patients.[3-5] Identified causes of this apprehension include lack of training, fear of intrusion, and fear of inadequate knowledge. Physician discomfort with patient sexuality results in inadequate sexual histories and subsequent gaps in patient care.

Common errors stem from assumptions made about patients' sexual behaviors and concerns. Doostan and Wilkes outline the scope of sexual dysfunction from differing chronic conditions.[3] In patients with invisible conditions, we might assume normal function and provide routine guidance regarding sexuality and family planning or, too often, forego any discussion of sexual concerns at all.

Society often views patients with more visible disabilities as sexually innocent. Outsiders and family alike may assume that they are unlikely to find sexual partners. Physicians can be guilty of these same assumptions and fail to address sexual concerns or provide education. We must consider the desire of families and caretakers to "protect" developmentally disabled patients from sexual predators by withholding sex education. At the same time, we must acknowledge that this decision can result in inappropriate sexual behaviors because sexuality is inherent in all people, regardless of disability.

Studies on adolescents with chronic conditions show the need to take sexual histories and provide sex education. Teens with obvious physical disabilities are undoubtedly sexually active.[6, 7] In a large survey of high school students by Suris et al., there were no differences between adolescents with and without chronic conditions on a number of factors including self-report of previous sexual intercourse, previous pregnancy, or contraceptive use.[7] This study also reported no difference between adolescents with visible versus invisible conditions; obvious disabilities might affect self-esteem and body image, however, and thereby influence relationships.

There is evidence that patients with physical disabilities receive inadequate education regarding marriage, family planning, sexually transmitted infections, and sexual abuse.[7, 8] These patients must, therefore, be at risk for adverse sexual consequences. Physicians must be careful to tailor education to patients' specific conditions, because "routine" courtship and sexual relationships are not necessarily the norm and inappropriate information might be harmful.

Medical education in human sexuality and sexual history-taking is often missing in both residency and medical school curricula.

It is our role to safeguard the health and well-being of our patients, however hard it is to overcome our biases regarding their illnesses and their sexuality. Physicians are comfortable addressing sexuality from the fact-based biomedical model, but when there is less science, we grow insecure in our roles as healer and teacher. If we are confident with our knowledge and expertise, we can more willingly and competently provide sexuality counseling.[8]

Medical education in human sexuality and sexual history-taking is often missing in both residency and medical school curricula. In a recent unpublished survey of primary care residents at our institution, most residents indicated that their training in patient sexuality was fair to poor in both residency and medical school. This is supported by the Maheux and Temple-Smith studies, in which physicians cited lack of appropriate training as a reason for inadequate sexual history-taking.[9] Physicians who received residency training in human sexuality provided better histories than those who did not.

Didactic discussion of human sexuality in the contexts of health promotion and specific illnesses is important, but actual practice and application of sexual history-taking and counseling play the larger role in

improving physicians' confidence. The use of standardized role-playing will allow trainees to apply techniques and information in a safe setting prior to confronting these issues with actual patients.

As primary care providers, we are not expected to conduct intensive interventions when sexual concerns arise. Often brief interventions make significant impacts on our patients. A commonly used brief intervention is the PLISSIT model developed by Annon,[10] with four progressive levels—(1) permission, (2) limited information, (3) specific suggestions, and (4) intensive therapy—that can guide assessments and interventions to improve sexuality in healthy and chronically ill patients. Broaching the topic of sexuality often gives patients permission to discuss their concerns and can be all that is needed to overcome barriers to healthy sexuality.

The conspiracy of silence around sexuality in the chronically ill and disabled is harmful and unnecessary. Increasing our comfort in discussing sexuality and routinely including sexual histories in our assessments will allow our patients to have more fulfilling lives.[11]

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Preventing fractures among people with developmental disabilities

Identifying high-risk individuals could reduce fractures

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People with developmental disabilities have a high risk of osteoporotic fractures due to a number of conditions that both diminish attainment of peak bone mass and/or increase susceptibility to falls. Most importantly, many of these factors represent modifiable risk factors and provide opportunities for prevention. An article recently published in this journal showed that adults with developmental disabilities residing in a developmental center in California had an increased rate of fracture (5.2 per 100 person-years) compared to the US population.[1] In this three-and-one-half-year study, an increased odds ratio of fracture was associated with age, white race, male gender, coexisting epilepsy, documented osteoporosis, and ambulatory status. Clearly the frequency of osteoporotic fractures in people with developmental disabilities underscores the importance of offering preventative measures.

With more therapeutic options for the prevention and treatment of osteoporosis, clinicians have expanded their view of the population at risk for osteoporotic fractures. In addition to postmenopausal women and octogenarians, we now contemplate surveillance and preventative therapies in patients on chronic oral glucocorticoid therapy,[2,3] patients undergoing pulmonary,[4] cardiac,[5] and renal transplants,[6] and men and women with syndromes of catabolic wasting. Recent clinical trials have demonstrated the efficacy of prophylaxis to prevent osteoporosis and reduce fracture risk in groups other than the postmenopausal women. Thus one could argue that, like other high-risk populations, people with developmental disabilities could be an important target for early diagnosis and treatment.

Once clinicians assess bone mineral density with densitometry and/or biochemical markers of bone turnover,

they can institute antiresorptive therapies to reduce the personal and economic burden of osteoporotic fractures. It is well recognized that fracture incidence is the product of dual risk profiles: bone mineral density and propensity for falls.

People who have developmental disabilities and are mobile share with aging men factors that can increase the probability of falling: balance impairment because of intrinsic motor coordination difficulties, an increased possibility of dizziness, hypotensive episodes secondary to medication use, and potential for loss of muscle bulk, hypotonia, and generalized loss of muscle strength.

The increased risk of bone density abnormalities in individuals with developmental disabilities is less obvious and can result from factors that influence either the attainment of peak bone mass or the probability of increased bone resorption. People with developmental disabilities often experience coexisting conditions that affect bone mineral content, including hypogonadotropic hypogonadism, growth hormone deficiency, Turner's syndrome, and thyroid abnormalities. Many are on drugs that reduce bone mineral density as well, including (1) psychotropic medications used for behavioral modulation, which cause dysregulation of the hypothalamic-pituitary-gonadal axis (presumably, by dopaminergic activity); and (2) drugs to treat epilepsy, which can either have adverse effects on bone mineral density and ultimately reduce osteoblast function and bone formation or promote increased bone resorption, further compromising skeletal health.[7] In the Lohiya et al. study[1], epilepsy was present in 30% of the study population and was thought to contribute to fracture morbidity. Dietary deficiencies and mobility impairment may further compromise the attainment of peak bone mass during critical years of bone formation. Inadequate exposure to sunlight in certain populations of institutionalized adults may contribute to vitamin D deficiency syndromes.

There is undoubtedly a critical need to evaluate residents systematically at developmental centers and to identify those people with bone mineral density abnormalities who might benefit from preventative therapies. In the current era of widely available diagnostic tests and well-tolerated therapies, any other strategy would be contrary to the consciousness and conscience of the caring physician and the prevailing precepts of public health.

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WJM focuses on adolescent health care

A call for papers

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The 36 million adolescents (10 to 19 years old) in the United States make up almost 14% of the total population. Although adolescents are in general healthy, roughly one fifth have some type of health problem. They are a unique group in terms of development and healthcare concerns, caught betwixt and between. Teens are beyond many of the acute illnesses of childhood and are only beginning to be affected by the chronic disorders of adulthood. Most of their health concerns are related to behavioral and environmental causes and are potentially preventable. Many practitioners may not realize recent trends.[1]

Demographic

Among the adolescent population in the United States, there is an increase in the total number of those living in single-parent families, those living in poverty, and those of minority status.[1]

Healthcare utilization

Teens utilize fewer healthcare services than any other group. They are the least likely to have health insurance.[1]

Mortality

Accidents, unintentional injuries, homicides, and suicides account for the greatest number of deaths among adolescents in the United States. Males die more often than females. Black males from 15 to 19 years old are 9 times more likely to die from homicides than are white males of the same age.[1]

Risk-taking

Adolescents are initiating risky behaviors at progressively earlier ages. Although over one third of high school students report being drunk in the past 30 days, teenage substance use[2] and smoking[3] have decreased somewhat, reversing the upward trend throughout most of the

1990s. Rates of first-time sexual activity have slightly decreased. Condom use has increased and births to teens have decreased.[4]

Violence

Overall, crime and violence by youth are declining. Violent juvenile crime arrests have fallen 25% since 1994.[5] Children and youth are at a much greater risk of being the victims than the perpetrators of a violent crime. Children and youth aged 12 to 17 are nearly 3 times as likely as adults to be victims of violent crime. Nine out of 10 schools experience no serious or violent crime on their campuses.[6]

Weapons

Of high school students surveyed in the 1997 Youth Risk Behavior Survey, 18.3% reported carrying a weapon within the 30 days prior to the survey. Among those, 5.9% of high school students carried a gun in the past 30 days, down from 26.1% in 1991.[5]

Violence on school property

The Youth Risk Behavior Survey reported that 8.5% of high school students carried a weapon on school property in the 30 days before. A total of 7.4% of students were threatened or injured with a weapon on school property in the 12 months prior to the survey.[5]

Exercise, diet, and health

Exercise decreases with increasing age. Only 28% of adolescents eat the recommended five or more servings of vegetables and fruits daily. As many as 60% report more than two servings of high-fat food per day.[1]

As noted, while there have been some improvements in the health of teens and a decrease in some risk-taking behaviors, violence and teen pregnancy are still unacceptably high. The recent violence in Colorado and Georgia focused the nation's attention on teen violence. Rather than treating this as an isolated, horrific incident, some have begun to characterize teens in general as violent. Youth are often unfairly treated in the media. Their strengths and accomplishments are rarely touted. "Today's middle-class and suburban teenagers are better behaved than kids of the past," writes one recent commentator. "Regardless of what dire theory of societal unraveling experts use to explain why two suburban Colorado teens went on a murderous rampage, a major fact is overlooked: the best evidence shows that rates of murder, school violence, drug abuse, criminal arrest, violent death, and gun fatality among middle- and upper-class teenagers have declined over the last 15 to 30 years."[7]

The Western Journal of Medicine plans to devote an entire issue to the subject of adolescence. We are specifically interested in articles that address the strengths of adolescence and discuss what is known about preventive factors and resiliency. We are looking for research papers, commentaries, scholarly reviews, or essays. Topics of special interest to us include:

- issues in pharmacology related to teens
- attention deficit hyperactivity disorder
- the psychological effects of obesity and the state of current treatment
- ethical issues related to emancipation, confidentiality, or reproductive health
- violence prevention
- the effect of divorce on teens
- evidence-based approaches to adolescent health issues.

We welcome submissions in any health-related area (medicine, nursing, social sciences, pharmacy, social work) from those who work with teens and from teens themselves. Please direct any questions to Martin Anderson, manderso@ucla.edu.

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We welcome articles up to 600 words on topics such as a memorable patient, a paper that changed your practice, your most unfortunate mistake, or any other piece conveying instruction, pathos, or humor. The article should be supplied on disc and/or emailed to wjmsf@pacbell.net. Permission is needed from the patient or a relative if an identifiable patient is mentioned. We also welcome quotations of up to 80 words (or less) from any source, ancient or modern, which you have enjoyed reading.

Mail

Stephen King wrist

To the Editors,

A 51-year-old white female presented to us complaining of pain in her left wrist that worsened with flexion of the left hand. The patient had been in otherwise excellent health but had noticed the pain on arising that morning. The pain made it difficult for her to do her household chores and also made it hard for her to concentrate on her graphic arts work, which demanded that she sit at a computer for up to 8 hours a day. This was the first time that the patient had experienced this pain, and there was no history of any trauma to this area. The rest of her medical history as well as her family's was equally noncontributory, and there was no history of any arthritides or neurologic disorders.

Subsequently, we recommended that if she must read in bed, she alternate hands in holding such tomes and do so quite frequently in order to give each hand a respite.

Physical examination revealed tenderness in the left wrist ventral area; the tenderness was localized and did not radiate. There was no shoulder or elbow tenderness nor any limitation of motion in these joints. Examination of the fingers revealed no effusions, heat, or tenderness. The pain was augmented in the left wrist area with flexion of the left hand, and there was some weakness of left hand grasp. The rest of the physical and neurological examination was not remarkable.

Upon further questioning, we learned that the patient had for the previous 3 nights been engrossed in the latest Stephen King thriller, a 702-page paperback novel. An avid reader, the patient preferred to read while in bed, holding the book in her left hand continuously for 2 to 3 hours before going to sleep. She stated that she had to hold the book tightly in her left hand in order to keep the pages of the book flat so they would not curl over.

We suggested that she stop this reading practice for a few nights and give the hand a chance to rest. By the second day of discontinuance, the pain completely disappeared. Subsequently, we recommended that if she must read in bed, she alternate hands in holding such tomes and do so quite frequently in order to give each hand a respite. If that did not work, we suggested that she use a small, portable podium to hold and support the book. Indeed, the patient has heeded our advice about changing hands, and we are happy to report that she has experienced no further problems and continues to perform all her daily activities without difficulty. Just to be on the safe side, however, she has purchased a small portable book podium to use if the pain ever recurs.

We call this condition a "Stephen King wrist." Mr. King, when contacted in Maine for permission to name this disorder after him, consented. He suggested, however, that "it could just as easily be called James Michener wrist!"

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Original Research

Attitudes after unintended injury during treatment: a survey of doctors and patients

ABSTRACT **Objective** To compare the attitudes of doctors and patients toward the disclosure of information after adverse medical events. **Design** Cross-sectional questionnaire survey. **Setting** Ophthalmology department of an outer London hospital. **Subjects** 246 patients attending one ophthalmic outpatient clinic during a 5-week period and 48 ophthalmologists. **Main outcome measure** Proportion of each group who believed that patients should be informed about the occurrence of an adverse event and its potential future complications following elective ophthalmic surgery. **Results** Most patients (226/246, 91.8%) believed that a patient should be informed of an adverse event. Fewer ophthalmologists (29/48, 60.5%, P<0.001; odds ratio 7.4 [95% CI 3.7-14.3]) shared this belief. The majority of patients (200/246, 88.5%) believed that a patient should be as fully informed as possible about the event and possible future complications, but this belief was shared by a minority of ophthalmologists (16/48, 33.3%, P<0.001; odds ratio 8.7 [95% CI 4.7-15.9]). **Conclusion** After an adverse medical event, there is a discrepancy between the amount of information that patients wish to be given and that which physicians feel is appropriate.

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Introduction

Unintended injuries or adverse events caused during treatment occur much more commonly than previously believed.[1] Recent legal and disciplinary cases have shown that although patients are increasingly dissatisfied with a perceived lack of openness in the medical profession, doctors in the United Kingdom are not legally obliged to provide an explanation after an adverse event.[2] Because of this situation, the General Medical Council (the regulatory body for doctors in the United Kingdom) has revised its guidance on good medical practice, stating that routinely, after an adverse event, a full and honest explanation and an apology should be provided.[3] To come to a fuller understanding of these circumstances, we surveyed the attitudes of both patients and doctors about doctors providing information to patients after a hypothetical adverse event during cataract surgery.

Subjects and methods

A specifically designed questionnaire (see box) was used to survey all patients attending a consultant ophthalmologist's clinic during 5 weeks in 1998. All 48 ophthalmologists attending a regional meeting participated; 246 of 302 (81%) patients also agreed to participate. The questionnaire asked about the postoperative information that should be provided routinely given a hypothetical situation in which a common intra-operative complication (posterior capsular rupture) occurred during cataract surgery, with an estimated 10% risk of an adverse effect on vision.

Results

The attitudes of the patients differed substantially from those of the ophthalmologists: 92% (226) of patients compared with only 60% (29) of ophthalmologists believed that a patient should always be told if a complication has occurred (P2=34.5, 1 df, P<0.001; odds ratio 7.4; 95% CI 3.7-14.3). The ophthalmologists who did not believe that patients should always be told responded either that the patient should never be told or that it depended on the circumstances. Altogether, 81% (200) of the patients but only 33% (16) of the ophthalmologists believed that a patient should be informed of a complication and be given detailed information on possible adverse outcomes (P2=47.1, 1 df, P<0.001; odds ratio 8.7; CI 4.7-15.9).

Discussion

Our survey shows that after an adverse event, patients expect to receive more detailed information than doctors believe should be given. Doctors' reluctance to provide patients with detailed information after adverse events is often an attempt to protect them from potentially detri-

Questionnaire

Please read the following story (which is typical but fictional):
Mrs. Brown has an operation for a cataract. During surgery, there is a complication. The lens capsule breaks, and the surgeon has to make a bigger cut than planned, use stitches, and put in a different style of lens implant. There is an approximately 1-in-10 chance that Mrs. Brown's vision will be affected by these changes.

The next day, she sees well and is pleased.

Should Mrs. Brown be told about the surgical problem?
Yes/No

If yes, do we discuss the possible consequences?
Yes/ Only if she asks/ No

Please comment on your decision on the back.

What is your age?
25 and under/25-60 years/over 60 years

mental anxiety. Doctors may also avoid talking with patients about adverse possibilities, however, because it is a time-consuming, difficult, and unpleasant task and because they fear losing a patient's trust and being blamed or, perhaps, sued. It has also been suggested that the current medical culture, in which error is often automatically equated with professional incompetence or inadequacy, makes admissions to either patients or colleagues difficult.[4] Many studies show, however, that failure to provide information, an explanation, and an apology increases the risk of litigation and erodes the patient-doctor relationship.[5] After an adverse event, patients want disclosure of the event, admission of responsibility, an explanation, an apology, and prevention of similar errors in the future; in some cases, they also want the offender to be punished and to obtain financial compensation.[5]

The practice of medicine can never be free of errors.[4] Changes are required in the attitudes of both patients and members of the medical profession, with a realistic understanding of the limitations of doctors and medicine and more blame-free openness between doctors and patients.

We thank Jeremy Joseph for his advice.

Contributors: The original idea for the study arose in a meeting of the three authors. GV and MH designed and piloted the questionnaire. All three authors collected data and wrote the paper. MH performed the statistical analysis. MH acts as the guarantor of the paper.

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COMMENTARY

Do physicians have a duty to disclose mistakes?

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If doctors believe they may have injured their patients in the course of medical treatment, should they tell the patients? The intriguing paper by Hingorani et al. reports on a survey of British ophthalmologists and ophthalmology patients on this point.[1] When asked whether a patient should routinely be informed about a significant complication of cataract surgery, posterior capsular rupture, 92% of the 246 patients surveyed said yes, but only 60% of the 48 physicians surveyed agreed. (Posterior capsular rupture may or may not be the result of avoidable physician error in any given case.) The British General Medical Council has recently concluded that, although British courts have not required doctors to disclose serious medical accidents to patients, good medical practice requires disclosure and an apology. Does that practice make sense in the United States?

In fact, courts in several states, including California, have long said that doctors have a duty to make such disclosures.[2] These cases come up in an odd context, namely when a patient seeks to extend the statute of limitations, the time limit for bringing a lawsuit, on the grounds that the defendant "fraudulently concealed" the accident. Fraudulent concealment usually requires some affirmative deceptive act by the defendant to hide his or her role in the plaintiff's injury, but when the defendant is a "fiduciary," charged with looking after patient's best interests, mere nondisclosure can become "constructive fraud" and thus stop the running of the statute of limitation. The same doctrine has been used to extend the statute of limitation in cases of alleged malpractice by lawyers.

This legal duty to disclose is obscure and seems never itself to have been the basis of litigation. Nor does it appear to have been the grounds for disciplinary proceedings against physicians. Do American physicians disclose adverse events to their patients? I can find no study of American physicians or patients similar to that of Hingorani et al., but there is surely reason to doubt that such disclosure is common.

Hingorani cites a variety of reasons given by physicians for not disclosing adverse events. These include the desire not to increase the patient's anxiety, concern about decreasing the patient's trust in the doctor, increasing the likelihood of litigation, and reluctance within the culture of medicine to admit mistakes—all reasons that exist to the same or a greater extent in the United States. The increasing use of patient satisfaction surveys by managed care organizations and physician groups adds yet another reason to avoid an embarrassing disclosure.

Should American physicians disclose adverse events to their patients? When the knowledge of the adverse event is relevant to the patient's future medical treatment or health status, the answer is clearly yes. If the adverse event requires some additional treatment, its existence becomes part of the explanation of, and informed consent for, the additional treatment. Similarly, if the adverse event means that the patient needs special monitoring in the future, the patient needs to know.

But must doctors disclose that the reason for the future medical treatment or monitoring is their own mistakes? And should disclosure be made if there are no continuing consequences for future medical treatment? In these cases as well, the answer should be yes. Putting patients'—or clients'—interests first is the essence of a fiduciary's duty. The bond between professionals and their clients should require com-

plete honesty and responsibility for errors whether the professional is a physician, a lawyer, or a tax accountant. The fiduciary should disclose what reasonable patients or clients would want to know under the circumstances. Reasonable patients will often want to know about significant problems in their treatment to plan future medical care, to consider litigation, or just to help decide whether to change doctors. Hingorani's patient survey showed that patients overwhelmingly expected disclosure of the posterior capsular rupture.

As Hingorani et al. indicate, disclosure may prevent further problems in some cases. Various studies show that good doctor-patient communications reduce the risks of liability. Patients who feel misled may well feel bitterness toward their physicians; patients who believe they have been dealt with honestly may be more willing to accept that in medicine, as in every other human activity, accidents happen. We cannot, though, jump to the happy conclusion that disclosure will always lead to sweetness and light. Some patient relationships will be shattered by disclosure, sometimes at great cost to the physician. The temptation not to disclose will often be great. An ethical requirement that will be met only by saints is of doubtful value; a full disclosure rule may ask more of American physicians than can be expected under the circumstances.

One response is to change the circumstances. Those circumstances include not only an expensive, sometimes arbitrary, and always unpleasant liability system but also cultures—both popular and medical—with unrealistic expectations for medical care. Mistakes will always happen, minimizing them requires accepting their existence and learning from them. The willingness to admit mistakes to patients (and to ourselves) should be not only an ethical requirement but a practical prerequisite to minimizing future errors. We should complement the ethical requirement to disclose error with a healthcare system that encourages disclosure rather than punishes it.

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1 Hingorani M, Wong T, Vafidis G. Patients' and doctors' attitudes to amount of information given after unintended injury during treatment. West J Med 1999;171(30).
2 See, for instance, Stafford v. Shultz, 42 Cal.2d 767, 776, 270 P.2d 1 (1954); Guy v. Schuldt, 236 Ind. 101, 138 N.E.2d 891 (1956); Nardone v. Reynolds, 333 So. 2d 25 (Fla. 1976); and Roberts v. Francis, 128 F.3d 647 (8th Cir. 1997) (applying Arkansas law).

Cirrhosis mortality and per capita consumption of distilled spirits, United States, 1949-1994: trend analysis

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ABSTRACT **Objective** To describe, evaluate, and suggest interpretations for an observed aggregate-level relation between trends in mortality from cirrhosis and per capita consumption of distilled spirits in the United States. **Design** Trend analysis using data on US cirrhosis mortality and per capita alcohol consumption. **Results** There is a consistent long-term trend relation between mortality from cirrhosis and per capita consumption of distilled spirits in the United States from 1949 to 1994. Two instances of comparatively sharp drops in the consumption of spirits in the 1940s generated mixed results in predicting changes in cirrhosis mortality. **Conclusions** An aggregate-level relation between trends in long-term cirrhosis mortality and the consumption of spirits falls considerably short of establishing a direct causal link between the two for individuals. Moreover, two sharp drops in the consumption of spirits generated only mixed results with respect to the short-term trend in cirrhosis. Nevertheless, the observed relation between the consumption of spirits and cirrhosis mortality merits further investigation.

Introduction

This paper presents new epidemiological evidence of an aggregate-level relation between trends in per capita consumption of distilled spirits and death from cirrhosis in the United States. Such data may help us understand why a long rise in the trend of deaths from cirrhosis after the Second World War unexpectedly fell after 1973, even as the trend in total per capita consumption of alcohol continued to rise until the early 1980s. Although evidence of an aggregate-level correlation between the consumption of spirits and death from cirrhosis falls short of showing a direct or causal relation between the use of spirits and the risk of cirrhosis for individuals, it suggests that there is value in pursuing further multidisciplinary investigations to discern the links between the consumption of specific alcoholic beverages and cirrhosis.

Mortality from cirrhosis in the United States rose by 75% from 1950 to 1973 (from 8.5 to 14.9 deaths per 100,000 population), accounting for 33,350 deaths in the peak year of 1973. After this time, cirrhosis mortality began a long slow decline, falling to 7.9 deaths per 100,000 by 1993, roughly half of the 1973 rate and marginally below the rate in 1950

Summary Points

- Cirrhosis mortality in the United States peaked in 1973, but alcohol consumption did not peak until the early 1980s.
- Both shifts in the distribution of US drinking patterns (which are not reflected in per capita consumption statistics) and the increase in the availability of treatment for alcoholism have been suggested as potential sources of the decline in cirrhosis.
- The trend in the consumption of distilled spirits from 1949 to 1994 shows a close aggregate-level association with cirrhosis mortality.
- This aggregate-level relation suggests that research is needed into the link between the effects of specific alcoholic beverages and cirrhosis.

(see Figure 1a). The reasons why cirrhosis mortality fell and why the fall started when it did are unclear.

A large fraction of cirrhosis mortality has long been associated in both medical and popular thinking with heavy drinking.[1,2] Do changes in American drinking practices account for changes in the trend? Per capita alcohol use also rose and then fell during the period after the Second World War, increasing by 38% from the late 1950s to 1980 (from a mean of 7.57 liters of absolute alcohol to 10.45 liters for the drinking-age population), then falling by 20% from the early 1980s to the mid-1990s (to 8.36 liters) (see Figure 1a). The order of the peaks in time in the two trends, however, is contrary to what would have been expected if the fall in alcohol consumption had caused the fall in cirrhosis mortality. The beginning of the decline in cirrhosis mortality in the mid-1970s preceded the beginning of the decline in alcohol consumption by 7 or 8 years, thus generating a transitional period (1973-1980) when cirrhosis mortality was falling but per capita alcohol consumption was still rising.

Changing alcohol consumption should not, therefore, be eliminated as a possible explanation for the decline in cirrhosis mortality that occurred after 1973 in the United States. At least three factors may complicate the apparent relation between drinking and cirrhosis mortality when viewed through the medium of aggregate-level trend statistics.[3,4] First, statistics on per capita consumption do not provide a direct measure of the frequency of heavy drinking in a population. For example, statistics on per capita consumption may show an increase from one year to the next because the pool of drinkers in society has expanded (say, to include more youthful drinkers) rather than because the frequency of heavy drinking has increased. Second, contemporaneous changes in the availability or the efficacy of treatment for heavy drinking or cirrhosis may account for discrepancies in trends between per capita consumption and cirrhosis mortality. For example, a significant expansion in the alcoholism treatment system in the United States in the 1970s may have led to a decrease in cirrhosis mortality even as new or younger drinkers continued to drive per capita consumption rates upward. Third, cirrhosis develops slowly, ordinarily requiring 15 to 20 years of heavy drinking before death occurs from the disease. Some analysts have suggested that changes in per capita consumption may require the passage of just as many years for the effects to be fully realized in changes in mortality from cirrhosis.[5-7] All three factors illustrate ways in which alcohol consumption may account for cirrhosis mortality even if the two societal trends are not always highly correlated.

No compelling evidence has emerged to show that the three factors we have noted actually account for the discrepancies in trends between total alcohol consumption and cirrhosis mortality. Survey data on trends in drinking patterns in the population do not indicate that a significant expansion in the pool of drinkers or a consistent decline in the frequency of heavy drinking occurred from 1973 to 1980.[8] Smart and Mann have suggested that the order of magnitude of the expansion in alcoholism treatment in the United States between 1979 and 1987 may have been sufficient to account for the concurrent decline in cirrhosis mortality.[9] Smart and Mann did not address the transitional period from 1973 to 1980, however, when consumption was rising and cirrhosis mortality was falling; moreover, their analysis has highlighted some of the methodological problems involved in attempting to equate increases in the availability of treatment programs directly with credible estimates of the supposed impact of treatment on cirrhosis mortality.[10] Although analyses based on time lags have been used to study data on discrepant consumption and changes in cirrhosis mortality in countries where changes in consumption preceded changes in cirrhosis—for example, in the United Kingdom[5] and Sweden[6]—the circumstance of a change in cirrhosis statistics preceding a change in consumption has worked against applying a similar approach to trends in the United States.

Another mode of linking cirrhosis mortality with alcohol consumption focuses on the relation between specific alcoholic beverages—distilled spirits, beer, and wine—and cirrhosis mortality. More than 30 years ago, Terris published an analysis of data on trends from the United States, Canada, and the United Kingdom suggesting that per capita beer consumption did not contribute to trends in mortality from cirrhosis.[11] Because wine consumption traditionally contributes only about one eighth of per capita total alcohol intake in the United States, Terris's exclusion of beer in his analysis implied that the consumption of spirits was the principal contributor to aggregate cirrhosis mortality. More recent studies have also drawn attention to the consumption of spirits and its relation to trends in cirrhosis mortality.[12-14] No paper has as yet examined either long-term data on trends in

the United States or the sharp short-term changes in the consumption of spirits that occurred in the 1940s.

Methods

Two kinds of relations in the trends between cirrhosis mortality and alcohol consumption were examined. First, we compared the long-term (1949–1994) relation between cirrhosis mortality and the trend in total per capita alcohol consumption in the United States (including the consumption of all types of alcoholic beverages). Then we compared the long-term relation with consumption trends for spirits, beer, and wine. Finally, we evaluated changes in cirrhosis mortality occurring after two comparatively sharp drops in the consumption of spirits in the 1940s.

Sources of data

Data on national cirrhosis mortality and per capita alcohol consumption were analyzed. Data were standardized by age to the US population in 1940, and total cirrhosis mortality for the 46 years from 1949 to 1994[15] was adjusted for the apparent impact of shifts in the coding of cirrhosis mortality in the International Classification of Diseases (ICD).[16] (Since this paper is published simultaneously in the BMJ, further information is available on the BMJ website.) The year 1949 was selected as the starting point for long-term trend analysis because, as Terris originally noted,[11] the introduction of the ICD-6 (6th revision) in 1949 had a comparatively large effect on the apparent mortality from cirrhosis; later revisions of the ICD had smaller and more easily corrected effects. Our use of total cirrhosis mortality, instead of the code for "cirrhosis with mention of alcohol," is common practice in the literature on the relation between alcohol and trends in cirrhosis; this approach reflects prevailing reservations about the validity of subgroup discriminations in the coding of cirrhosis mortality.[17] Our particular focus on the question of whether the change in cirrhosis mortality may be accounted for by changes in alcohol consumption also allowed for the use of the total cirrhosis mortality variable.

Total per capita consumption and figures for the consumption of specific beverages are expressed in absolute alcohol equivalents, which were calculated in our source by dividing the total number of gallons sold by estimates of the alcohol content of specific beverages and then by estimates of the population, aged 15 and older (before 1971) or 14 and older (1971-1994).[18] Although the mean alcohol content of distilled spirits declined marginally after 1973, our estimates of the consumption of spirits have not been adjusted for this factor.[19, 20]

RESULTS

Time series analysis, 1949–1994

The trend in cirrhosis mortality is compared with the trends in four variables of alcohol consumption (total

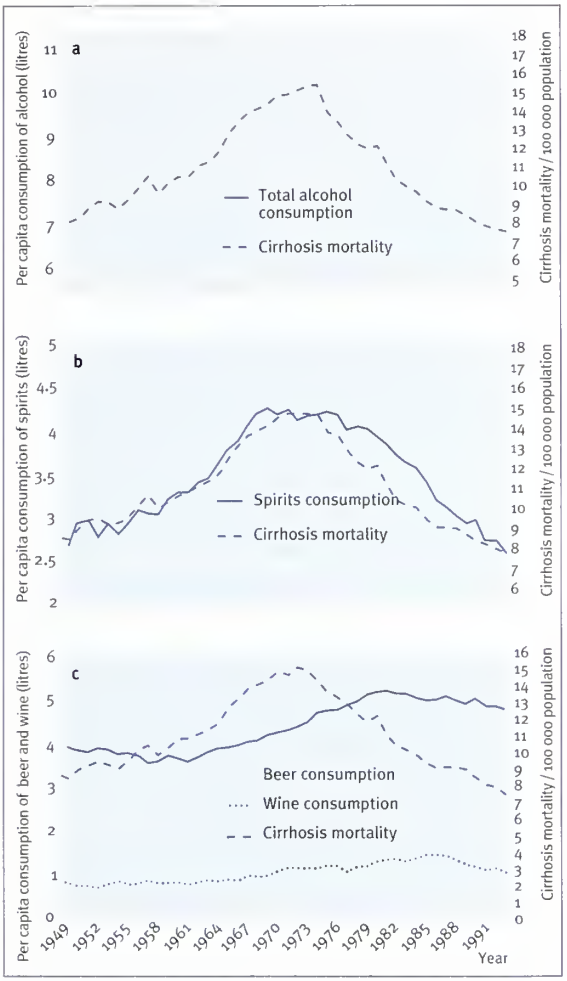

Figure 1 *Mortality from cirrhosis and total per capita consumption in the United States, 1949-1994, of (a) total alcohol, (b) distilled spirits, and (c) beer and wine*

alcohol consumption, spirits consumption, beer consumption, and wine consumption) in Figure 1. These curves show that the consumption of spirits has a stronger association with cirrhosis mortality than the total per capita consumption of alcohol, beer, or wine. Pearson's product moment correlation coefficient expresses the degree of covariation in a pair of standardized variables. The relation between the consumption of spirits and cirrhosis mortality generated the highest correlation coefficient (spirits, r=0.94; total alcohol, r=0.50; beer, r=−0.03; wine, r=0.05).

Autoregressive integrated moving average models provide a more sophisticated statistical approach to the evaluation of trend data.[21, 22] These models assess associated trends for the impact of current and past values of the independent variable and for a dependent variable's impact on itself. Two autoregressive models were developed: one for the relation between the consumption of spirits and cirrhosis mortality and the other for the relation between total alcohol and cirrhosis mortality. The

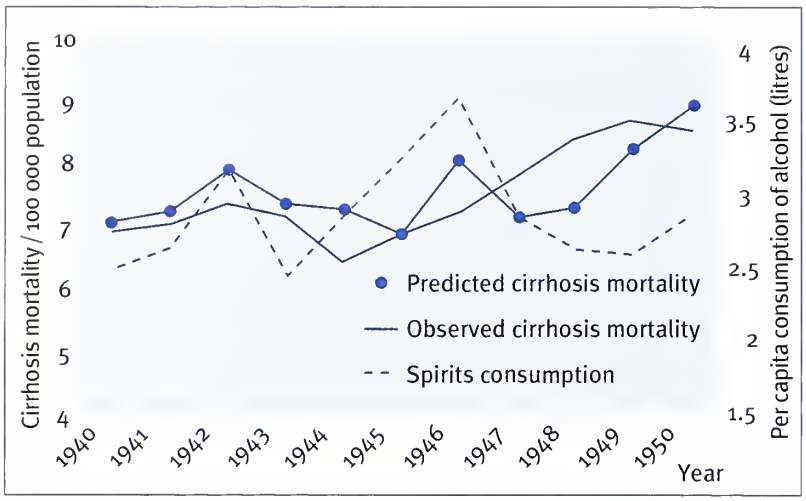

Figure 2 *Per capita consumption of spirits, predicted mortality from cirrhosis (adjusted), and observed mortality from cirrhosis in the United States, 1940–1950*

model for spirits generated a better predictive fit than the total alcohol model (spirits model, adjusted r^2=0.47; total alcohol model, adjusted r^2=0.32). Both models used only short-term, lagged effects (consumption in current year, previous year, and the year before that). (Additional information is available on the BMJ website.)

Drops in the consumption of spirits

Epidemiologists have long been wary of aggregate-level correlations between a pair of long-term slowly changing trends—like the observed correlation between cirrhosis mortality in the United States and the consumption of spirits during 1949-1994—because of the possibility that unmeasured third factors may account for both trends. In the period immediately preceding our long-term analysis, there were two relatively sharp 1-year drops in the consumption of spirits, one occurring from 1942 to 1943 and the other from 1946 to 1947. These provided an opportunity to examine whether the aggregate-level association derived from the longer-term trends could predict the impact of changes in the consumption of spirits on cirrhosis mortality in the more demanding environment of sudden and marked change in the variable for the consumption of spirits.

The apparent per capita consumption of spirits fell by 22% from 1942 to 1943 and by 23% from 1946 to 1947. These are the only instances of 1-year drops in the consumption of spirits in the 1940s and the only instances of comparatively large 1-year declines in the consumption of spirits from 1940 to 1994. By comparison, there were 20 instances of 1-year declines in the consumption of spirits from 1949 to 1994. Among these, the mean drop in consumption was 3%; 18 of the 20 were declines of less than 5%; and the 2 largest declines were of less than 10%. Because the consumption of spirits and rates of cirrhosis before 1949 did not contribute to the construction of the model for spirits, the sharp declines in the consumption of spirits in 1942-1943 and 1946-1947 represent fresh data, suitable for independent testing of the model's ability to predict trends in cirrhosis mortality.

The two predictive tests generated only mixed results, however. Figure 2 plots the consumption of spirits, the model's predicted cirrhosis curve, and the observed cirrhosis curve from 1940 to 1950, adjusted to ICD-9 coding. We have used the "static" predictive mode, which allows the model to make its prediction of cirrhosis mortality for each successive upcoming year, using the observed cirrhosis mortality in the preceding year and the observed amount of spirits consumed in the current year, the previous year, and the year before that. This requires that the model be given sufficient lead time to establish its frame of reference for predictions. We have satisfied this requirement by starting the model in 1938, 5 years before the first sharp drop in the consumption of spirits (1942-1943). Both drops in consumption followed periods of rising consumption, and hence the model's predictions for the time after the drops included the lagged effects of the previous rising trend.

The model for the consumption of spirits seems to perform reasonably well in relation to the first sharp drop in consumption (1942-1943); it correctly predicts a downward trend for cirrhosis in 1943 and 1944. The predicted curve is displaced upward, however, by the model's over-prediction of a rising trend in cirrhosis for 1942-1943. The model also places the lowest point of the fall in cirrhosis after 1942 in 1945, 1 year after the lowest point was actually reached. The model's predictive performance in relation to the second sharp drop in spirits consumption (1946-1947) is considerably less successful. The model predicts a sharp decline in cirrhosis in 1947, a slight upward rebound in 1948, and a steep upward trajectory in 1949 and 1950. In fact, cirrhosis mortality climbed steeply in 1947 and 1948. The change in cirrhosis mortality in 1949 occurred after the change from ICD-5 to ICD-6. A sharp decline in unadjusted cirrhosis mortality in 1949 is eliminated once the unadjusted 1949 mortality is adjusted to the ICD-9 standard.

Some cautions should be noted in connection with these two tests of the model for the consumption of spirits. The decline in the consumption of spirits in 1942 occurred during the Second World War as a result of the US War Production Board's commandeering of all distilled spirits to wartime uses, such as the production of synthetic rubber and explosives.[23] Widespread wartime hoarding of scarce consumer goods may have altered the usual peacetime relation between consumer purchasing and the actual consumption of spirits.[24] The decline in the consumption of spirits in 1946-1947, moreover, may have reflected a broad shift from wartime to postwar consumer behavior, thus also introducing a measure of unreliability into the usual relation between purchasing and actual consumption. Also,

time-series analyses address the description of statistical regularity over many years of data, and so spot-checks of predicted and actual results for short-term trends do not definitively confirm or negate the trend models.

Discussion

What sort of connection between the consumption of spirits and cirrhosis mortality is suggested by the data we have presented? Several possibilities should be considered. Spirits consumption in itself may not be "doing the work" in the observed relation. Instead, the amount of spirits consumed may be acting as an indicator of the changing acceptability of heavy drinking in American society. The consumption of spirits may also have gained a special aggregate-level relation with cirrhosis by being the preferred beverage of heavy drinkers or alcoholics.[25] Our data also do not exclude the possibility of an underlying cohort effect in which the rise and fall of cirrhosis mortality before and after 1973 represent the "mortality trail" through its course in an American generation of comparatively heavier drinkers who prefer spirits. The possibility of a direct relation between the consumption of spirits and risk of cirrhosis is not specifically excluded either. The higher alcohol concentrations of spirits (in unmixed drinks) and the potential for causing a faster rise in blood alcohol concentrations may give rise to comparatively greater hepatic insult and damage.[26] Such an effect would be exacerbated if, as has been reported, those who drink spirits tend to consume greater mean amounts of alcohol per drinking occasion[27, 28] and more often drink without eating.[29, 30]

Conclusion

The reported aggregate-level relation between the consumption of spirits and cirrhosis mortality in the United States cannot be directly generalized to other nations, even to wine-drinking cultures with historically high rates of cirrhosis. Therefore, this finding is context-specific. It also suggests the value of paying further attention to contextual factors in the relation between alcohol and cirrhosis. Nevertheless, the observed aggregate-level relation in the United States undoubtedly warrants more investigation. Additional epidemiological and biomedical research is needed into the cirrhosis-causing effects of specific alcoholic beverages.

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Contributors: RR initiated the research with his observation of the stronger association between the consumption of spirits and mortality from cirrhosis. He was responsible for many of the core ideas and for writing the paper. WCK was responsible for generating the ARIMA results and participated in some of the writing. KMF participated in discussions concerning core ideas and the writing of the paper. All authors act as guarantors of the paper.

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COMMENTARY
Societal changes could also be to blame

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With their exploration of the relationship between ethanol use and death from cirrhosis, Roizen, Kerr, and Fillmore investigate an important and prevalent public health concern. Of the 26,000 deaths in the United States each year due to liver cirrhosis, it is estimated that 40% to 90% of these cases have a history of alcohol abuse,[1] making research in ethanol consumption trends important for understanding the development of cirrhosis.

Despite its demonstrated detrimental effects, ethanol consumption does not entirely explain occurrences of serious liver disease, suggesting a role for other variables. Previous investigators have noted a low incidence of serious liver disease in alcoholics and no link between ethanol consumption and severity of disease past a threshold intake.[1] The pathogenesis of liver disease likely involves environmental and hereditary factors, including variation in ethanol metabolism and nutrition. One variable that has received recent attention is the presence of the hepatitis C virus. While the exact nature of the link has not been established, it is generally accepted that patients with hepatitis C develop liver injury at a younger age and with greater severity.[1,2] Hepatitis C can be accelerated by ethanol use and increases the incidence of chronic liver injury in alcoholics. There is a high incidence of HCV infection in alcoholics, approximately 18% to 25%, with an even greater occurrence in alcoholics with serious liver diseases.[1] This can be explained in part by the prevalence of illicit drug use among alcoholics, although a disproportionately high number of alcoholics with no history of drug use also have hepatitis C.[2]

Roizen et al. have discovered a striking long-term temporal correlation between spirits consumption and cirrhosis mortality. As the authors note, however, serious liver disease leading to cirrhosis mortality develops following 15 to 20 years of heavy drinking, so the simultaneous rise in cirrhotic mortality and spirits consumption cannot be a causal relationship. Spirits consumption may, however, serve as a marker for some other event that occurred 15 to 20 years earlier and consequently affected cirrhosis mortality. Societal changes such as advertising, the inclusion of women in the work force, and population demographics may affect ethanol consumption, spirits consumption, and cirrhotic mortality. For example, the rise in total ethanol and spirit consumption beginning in the early to mid-1960s corresponds with the baby boom generation reaching young adulthood, not only swelling the ranks of ethanol consumers but also lowering the average age of drinkers.

The statistical relationship found in this study is complicated by the variables previously mentioned as well as by possible confounders. This study compares total national spirits consumption with cirrhosis deaths. This approach allows the greatest scope and objectivity and offers a first look at possible causal relationships between classes of alcoholic beverages and the development of liver cirrhosis. Total spirits consumption, however, does not take into account that only a small proportion of individuals who consume ethanol consume enough to put themselves at risk for cirrhosis. The rise in cirrhotic death more likely signals changes in the consumption patterns of heavy drinkers, who may have preceded the general population in shifting toward spirits consumption. The statistical association is further confounded by the proportion—over 50%—of heavy drinkers who do not develop serious liver disease[1] and by nonalcoholic cirrhosis mortality.

Future studies should endeavor to account for the discrepancy between Roizen's intriguing observation that spirits consumption and cirrhotic mortality are temporally related and for the expected 15-to-20-year time lag that would be expected based on current understanding of the pathophysiology of ethanol-induced cirrhosis.

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capsule

Walk faster with implanted defibrillator Patients with implanted cardioverter defibrillators will come to no harm walking through electronic surveillance systems, as long as they don't dawdle, say a team of US cardiologists (Circulation 1999;100:387-392). A slow walk through three antitheft systems went undetected by the implantable devices in 169 volunteers, but seven showed evidence of clinically important interference when subjects stood close to a gate transmitter for two minutes. The take-home message for retailers is that they must signpost their systems better to avoid accidents.

Oral contraceptive use associated with myocardial infarction and ischemic stroke but not angina

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Br J Obstet Gynaecol 1998;105:890-896.

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Question
Is the risk of cardiovascular disease increased in women who take oral contraceptives?

Design
Cohort study with up to 26 years of follow-up.

Setting
Seventeen family planning clinics in England and Scotland.

Participants
A total of 17,032 women who attended a family planning clinic between 1968 and 1974 were included in the study. Women were included if they were married, white, had British citizenship, and were between 25 and 39 years old. Participants were sent annual questionnaires that requested information on their method of contraception, past medical history, social history, and height and weight. Altogether, 15,292 women (90%) were still participating at age 45, at which time they were sent a questionnaire that also requested information on smoking status.

Assessment of risk factors
At age 45, women were categorized as never-users of oral contraceptives (OCs) (n=5881), users of OCs for >8 years (n=3520), or users for ≤8 years (n=5891).

Main outcome measures
Myocardial infarction (MI), angina, ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and transient ischemic attack. The rates were adjusted for age, social class, smoking, and obesity (all diagnoses) and for parity (MI and angina). A restricted analysis was done, excluding women with hypertension, diabetes, or hyperlipidemia.

Main results
No association between the use of oral contraceptives and myocardial infarction was seen in the whole study population. When women with hypertension, hyperlipidemia, or diabetes were excluded (restricted analysis), an increased risk of MI existed among women who used OCs for up to 8 years (relative risk [RR] 1.9, 95% confidence interval [CI] 1.0-3.5). In further analyses, this risk was seen only in heavy smokers (≥15 cigarettes/day). In heavy smokers, the RR for MI in ever-users of OCs was 4.2 (95% CI 1.4-16.6), or for every 1060 heavy smokers taking OCs, one additional MI occurred per year. The risk of angina was generally similar in OC users and never-users. The risk of ischemic stroke was increased in current users. After adjustment for age, social class, smoking, and obesity, the RR was 2.4 (95% CI 1.1-5.1); the adjusted RR after restriction was 2.9 (95% CI 1.3-6.7), or 1 additional stroke per year for every 5880 OC users.

Conclusion
Oral contraceptive use was associated with an increased risk of myocardial infarction in heavy smokers. Current use was associated with a small increase in the risk of ischemic stroke.

COMMENTARY
Joy Melnikow, University of California at Davis, Sacramento, CA

Stroke and myocardial infarction are rare events among women of reproductive age. Prospective examination of the effects of oral contraceptives on these outcomes requires large cohorts and long follow-up times. Women already known to be at risk of stroke or myocardial infarction are unlikely to be prescribed oral contraceptives, which makes it difficult to define their effects on women with risk factors for cardiovascular disease. Because the estrogen dose in oral contraceptives has progressively decreased over the past 30 years, it is even more complicated to apply results from older studies to women using the current oral contraceptives.

This study is one of several recent reports revisiting the cardiovascular effects of oral contraceptives.[1-4] This study, with more than 20 years of follow-up and over 300,000 woman-years of observation, is well-suited for rare events. It is not much help with understanding the effects of current low-dose estrogen oral contraceptives because 68% of the woman-years of exposure are from oral contraceptives containing 50 µg of estrogen. It can, however, serve with other reports to establish a benchmark for the worst cardiovascular effects of oral contraceptives in healthy women. Another recent study suggests that lower-dose oral contraceptives may not increase the risk of myocardial infarction, even among smokers,[3] although women who use low-dose oral contraceptives and who smoke are at an increased risk of stroke.[4]

For nonsmokers with normal blood pressure, the risk of myocardial infarction is not affected by oral contraceptive use. An increased risk of myocardial infarction is confined to women smoking ≥15 cigarettes per day.

In contrast, the health risks of smoking are enormous. Clinicians need to help patients quit smoking and to work together for public health regulations that make it harder for young people to start.

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Oral methylprednisolone improved symptoms and disability resulting from attacks of multiple sclerosis

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Question

In patients with multiple sclerosis, how effective is oral methylprednisolone in dealing with new symptoms or the recurrence of previously existing symptoms?

Design

Randomized double-blind placebo-controlled trial with 1 year of follow-up

Setting

A university hospital in Denmark

Participants

A total of 51 patients, 18 to 59 years of age (median age 37 years, 63% women), who had relapsing-remitting multiple sclerosis, with an attack of MS lasting >24 hours and <4 weeks. Exclusion criteria were receipt of glucocorticoid treatment within the past month, receipt of disease-modifying drugs within the past 6 months, pregnancy, lactation, diseases precluding glucocorticoid treatment, or any degree of spontaneous remission. Altogether, 98% of the patients completed the treatment.

Intervention

Patients were stratified according to scores on the Kurtzke Expanded Disability Status Scale (EDSS) and allocated to methylprednisolone (n=26) or to placebo (n=25). Methylprednisolone was given at a dose of 500 mg/day for 5 days and then tapered for the next 10 days.

Main outcome measures

Neurological disability was measured by changes in scores on the Scripps Neurological Rating Scale (NRS) and the EDSS. Severity of symptoms was measured using a 100-mm open visual analog scale (VAS). Patients also completed a questionnaire that assessed treatment effects.

Main results

Patients who received methylprednisolone showed greater improvement from baseline in NRS scores at 3 weeks (increase of 8 points vs 1, P=0.01) and at 8 weeks (increase of 11 points vs 0, P<0.001) than did patients who received placebo. VAS scores improved more after 8 weeks in patients who received methylprednisolone than in patients who received placebo (increase of 19 points vs 1, P=0.005). More patients who received methylprednisolone indicated improvement than did patients who received placebo (P=0.05). At 1 year, more patients in the methylprednisolone group showed improvement in scores on the EDSS than did patients in the placebo group (P=0.04) (see Table 1). Improvement in NRS and VAS scores did not differ between groups.

Conclusion

Oral methylprednisolone was effective in improving symptoms and disability associated with attacks of multiple sclerosis.

Table 1 *Methylprednisolone versus placebo for symptoms of multiple sclerosis at 1 year*

Outcome	Methyl-prednisolone (%)	Placebo (%)	Relative benefit increase* (%, 95% CI)	Number needed to treat (CI)*
>1 point improvement on Kurtzke Expanded Disability Status Scale	50	22	130 (3.3-454)	4 (2-105)

*Calculated from data in article.

COMMENTARY

Jock Murray, Dalhousie University, Halifax, Nova Scotia, Canada

The study by Sellebjerg and colleagues suggests that a method more convenient than intravenous therapy exists for treating acute attacks of multiple sclerosis and that it is more effective than no therapy. Recent positive trials have made high-dose intravenous methylprednisolone the standard treatment, although there are some who are unimpressed with the margin of benefit and do not treat most acute attacks. Others use lower dosages of oral steroids despite a lack of evidence of efficacy. This study suggests that dosage may be the issue.

Although this trial indicates that it may be practical and efficacious to treat patients with high-dose oral methylprednisolone, results in previous trials have varied. Confirmation with a larger, longer trial is necessary. Are the results of this 15-day treatment as effective as the standard 3- or 5-day course of intravenous treatment? Is the 10-day step-down method used in this study necessary? Could the positive results be related to the placebo group doing worse than expected and to some unblinding in the treatment group, resulting from adverse events in most treated patients?

Results from the North American optic neuritis treatment trial suggested that the use of low-dose oral steroids may reduce the time to the next attack;[1] there was also a trend toward more attacks in the year after treatment. Although the EDSS scores, but not those of the NRS or VAS, suggested that disability might be reduced in the treated group 1 year later, assessment at 1 year was not a primary outcome of the trial.

Many are unimpressed with the results of steroid use in acute attacks, but this study suggests that in untreated patients the rate of spontaneous recovery is low, which justifies treatment.

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Review: bias may contribute to association of vasectomy with prostate cancer

Question

Is the risk of prostate cancer increased in men with a history of vasectomy?

Data sources

Accounts from 1985 to 1996 were identified in MEDLINE, EMBASE/Excerpta Medica, and IME (Spanish Index Medicus) using terms relating to vasectomy, prostate, prostatic, and cancer. The bibliographies of relevant articles retrieved by the search were reviewed. Searches were also done in Research Activities published by the US Agency for Health Care Policy and Research and in the Spanish network of Research Transfer Offices.

Study selection

Epidemiological studies were selected if they measured the association between vasectomy and prosrate cancer.

Data extraction

Data were extracted on study design, setting, and period; time during which research was done; sample size; instrument used for gathering exposure and outcome data; effect of measurement units; srrength of association; and statistical methods. Possible sources of bias were confounding, selection, detection, nonresponse, regression to the mean, exposure recall, and disease misclassification. The merhodological quality was assessed by two independent investigators.

Main results

A total of 14 studies were included (5 cohort studies and 9 case-control studies). An excess risk of prosrate cancer was found in 11 studies; in 6 studies it was statistically significant. The weighted age-adjusted relative risk (RR) for prostate cancer across the 14 studies was 1.23 (95% confidence interval [CI] 1.01-1.49). The results of the studies varied widely. The sources of heterogeneity identified were type of design, study setting, presence of detection bias, and inadequate selection of controls. The weighted relative risk of prostate cancer in the cohort studies was 1.13 (95% CI 0.84-1.52) and in the case-control studies was 1.36 (95% CI 1.04-1.79). The RR of prostate cancer in the nine population-based studies was 1.12 (95% CI 0.96-1.32) and in the five hospital-based studies was 1.98 (95% CI 1.37-2.86). In studies in which detection bias was possibly presenr, the RR was 1.91 (95% CI 1.4-2.6); in those in which detection bias was less likely, the RR was 1.11 (95% CI 0.96-1.29). Studies with an adequate selection of controls had an RR of 1.11 (95% CI 0.94-1.31); those with possible selection bias had an RR of 2.24 (95% CI 1.42-3.54).

Conclusions

Meta-analysis of five cohort studies and nine case-control studies shows that there is an excess risk of developing prostate cancer in men who have had a vasectomy. Many sources of bias exist among the studies, however, leading to a probable overesrimation of the association.

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J. Latour-Pérez,
F. Pradas-Arnal,
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1998;70:191-200.

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COMMENTARY

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Bernal-Delgado and colleagues have summarized data on the relation between vasectomy and prostate cancer from 14 epidemiological studies composed of more than 200,000 men. The authors made a comprehensive search for published studies (but did not include unpublished work), and they evaluated each study for potential bias. They tabulated the results separately for cohort and case-control studies (because case-control studies often show stronger associations than actually exist) and stratified studies for other potential sources of bias. The most rigorous studies generally showed only a weak association between vasectomy and prostate cancer.

The studies included in this meta-analysis investigated the relation between vasectomy and the diagnosis of prostate cancer, not the occurrence of prostate cancer. Men who have had vasectomies are more likely to seek regular medical care than men who have not, and they are therefore more likely to have screening for prostate cancer (Sackett's "diagnostic access" bias[1]). Because none of the included studies attempted to control for medical care-seeking behavior, there is likely an exaggerated association between vasectomy and prostate cancer.

Does this meta-analysis exonerate vasectomy? Not necessarily. Given the popularity of vasectomy (approximately 25% of men 40 to 60 years old in the United States have had one) and the high prevalence of prostate cancer (>18% of men in their 60s[2]), even a small increase in the risk of clinically evident disease could have a large effect on public health.

Future epidemiological studies will probably not resolve this issue; randomized trials are, of course, not an option. Understanding the pathophysiology of prostate cancer may be our best hope for resolving this and other thorny questions about its causes.

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Best Practice

EVIDENCE-BASED CASE REVIEW

Treating the developmentally disabled

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Objectives

1. Explore our biases and stereotypes with respect to people with developmental disabilities
2. Understand techniques for caring for people with disabilities
3. Understand patient and family expectations
4. Understand the importance of preventive health care for patients with disabilities
5. Explore techniques to enlist other healthcare providers, the family, or the guardian in assisting and providing health care
6. Explore ethical and management controversies that arise in caring for people with disabilities

INTRODUCTION

Despite advances in medicine over the past half-century, people with developmental disabilities still face formidable obstacles in obtaining quality health care. Difficulties arise from multiple sources. These patients can be frustrating to treat because of complexities in communication, examination, and management. They are expensive in terms of time and resources, and legislators have had difficulty responding to problems of reimbursement and healthcare system fragmentation. Favorable societal perceptions of disabilities have been slow to evolve and, not surprisingly, physicians and other healthcare workers share many of the fears, biases, and stereotypes held by other members of society. Moreover, the literature documents the significant positive, or negative, effects that attitudes exert on health outcomes.[1,2] Improvement in physicians' attitudes and skills can significantly decrease the frustration and pain felt by patients with developmental disabilities and their caretakers. Therefore, given the lack of exposure in traditional medical curricula to the needs of patients with developmental disabilities and the status quo of our healthcare system, it is worth reviewing an approach to caring for these patients.

PREMISES

1. People make assumptions about people with disabilities that may not be accurate.
2. Physicians may feel uncomfortable or uneasy with patients with disabilities.
3. Patients with disabilities can be unable to cooperate because of deficits in physical ability, cognitive ability, or both. They typically demand more of clinicians' time and effort.

METHODS

In writing this paper, we used a variety of sources of information. Our primary source was focus group meetings with groups of developmentally disabled patients and/or their caretakers, organized with the help of Lanterman Regional Center in Southern California. We also conducted and videotaped interviews of individuals with developmental disabilities with their caretakers and/or families. We conducted an extensive literature search using MEDLINE (1990-1998), including the following terms in our search: developmental disability, disability, and mental retardation. We also contacted leading experts in the field by phone or email.

Case study

T.R. is a 22-year-old woman with developmental disabilities. Her baseline health is fair, and she has had no recent hospitalizations. She is severely retarded, nonverbal, and has great difficulty with motor control, but she can walk with the help of her mother, who accompanies her today. Her mother describes her daughter as follows: "T.R. is like a 2 year old. I mean she understands the things that a 2 year old understands. Even though she doesn't look like a 2 year old, that's the way that we think of her." T.R. awaits your attention for a routine history and physical exam.

What is meant by "developmental disability"?

There is not one standard definition of developmental disability nor is there general acceptance of this or other terminology. In New Jersey, for example, developmental disability is broadly defined as an inability, which started before 22 years of age, to be independent in two or more activities of daily living (ADLs).[3] People with developmental disability may be either cognitively or physically disabled or both. They may have mental retardation, autism, cerebral palsy, spina bifida, or a combination of these, or some entirely different condition. Moreover, classifications such as "mental retardation" are not unitary, neatly circumscribed entities; there exists wide-ranging causal heterogeneity. Developmental disabilities are a large and nonspecific classification of disease into which many conditions fall.

Would T.R.'s health be better served in an institutional hospital?

A few decades ago, a large proportion of people with developmental disabilities were institutionalized. Though segregated from the rest of society, they were able to receive the attention of healthcare teams accustomed to their special needs. This is no longer the case. A major restructur-

ing took place in the 1980s, and many disabled patients were de-institutionalized. Comprehensive plans to ensure that they continued to receive proper care were neither legislated nor enacted; it was thought that existing community service and healthcare organizations would be able to tend to their needs.[4-6] Doctors who had little experience or training in the special needs of patients with developmental disabilities were thrust into the role of providing their care. Typically, the result was wholesale dissatisfaction.

T.R.'s mother seems tense and impatient in the waiting room. What has prompted her frustration?

In our research, we heard from family members that caring for a loved one with disabilities and searching and pushing for quality health care for that relative cause a great deal of stress. Caretakers arm themselves with medical information before seeking medical advice, so they can make specific demands during consultations. Moreover, they find many physicians do not support the "rationale" for seeking elective care for someone who may never read or write, let alone "contribute to society." Resources permitting, they drive long distances to see physicians and dentists reputed to be responsive to their needs. Some even seek pediatricians to care for their adult relatives, because pediatricians are more accustomed to dealing with nonverbal patients.

Patients and caretakers tend to perceive physicians as insensitive to the special needs of the developmentally disabled and unprepared to care for them. The obstacles are many. Barriers to properly examining their loved one (lack of cooperation, hostility, fear, ignorance) and to collecting histories (nonverbal patients, uninformative family member, no old records) lead to incomplete investigations and thus deficient preventive care. The office environment, with its needles, intrusive exams, fluorescent lighting, and long waiting room stays, can be intolerable to the mentally and physically disabled and, consequently, to their caretakers.[7] As a consequence, many complain that anticonvulsant drugs and other medications do not receive proper monitoring. In the face of such complexities, caretakers have tremendous difficulty finding and retaining physicians and dentists willing to care for their relatives.

Has our managed healthcare system further aggravated caretakers' frustrations?

Our current healthcare system is not designed to handle the care of the disabled comfortably. Managed care emphasizes efficient, quick outpatient visits, which are often not possible with developmentally disabled patients. These patients can require far more than the allotted time and help from ancillary staff. They can be difficult to speak with and, when cognitively disabled, may resist or fight with the examiner. In spite of these known difficulties, reimbursement is typically low, often dependent on Medicaid

Francis Baggetta reads her daughter Nina a story.

Table 1

Barriers to effective care for the developmentally disabled

Difficulty of cognitively impaired patients

Cognitively impaired patients
- may not be able to communicate history or symptoms.
- may be unable to tolerate waiting room stay.
- may be threatened by aspects of the office or hospital environment such as needles, physical examination of private areas, unfamiliar clinicians.
- may resist or fight when confronted with an examination.
- may require ancillary or family help for even the smallest procedure.

Overall, H&P typically requires 3 times longer than average.

Difficulty of physically impaired patients

Physically impaired patients
- may require ancillary help to gain position, because many patients (despite normal intelligence) are severely compromised in movement.
- similarly, may have severe communication difficulties.
- because of their appearance and/or "unintelligible" speech, are misperceived as cognitively impaired.

Attitudes of healthcare professionals

Providers of care
- may not have had proper training to see difficult patients; training programs and curricula may not have emphasized or even included these patients' special needs.
- hold negative attitudes toward caring for the disabled, based on fear/apprehension or a few time-consuming and difficult personal encounters.

The healthcare delivery system
- is ill-equipped to handle the deinstitutionalized patient population.
- is inadequately reimbursed by Medicaid, Medicare, and/or private insurance agencies that do not recognize the greater time and effort required to provide adequate care for the developmentally disabled.

Summary points

- Patients with developmental disabilities and their caretakers are a population unaccustomed to satisfying treatment.
- The physician's obligation is to use strategies to recognize, accept, and then restrain any negative feelings for the patient.
- Our current healthcare system is not designed to comfortably handle the care of the disabled. Managed care emphasizes efficient, quick outpatient visits, which are often not possible with developmentally disabled patients.
- Enhancing communication is the key element in caring for the disabled.
- Informed consent requires, by definition, a mentally competent decision-maker. In cases of cognitive disability, though, it may be difficult to determine competence.

or Medicare payments that hardly compensate for the extra time and effort needed to give them proper care. It becomes quite costly to see such patients; therefore, many clinicians refuse. Those who do accept such patients may not necessarily be the most qualified to do so. Overall, guardians of patients with developmental disabilities must deal with a healthcare system not attuned to their needs.

In the waiting room, T.R. begins to make strange clicking and gurgling noises, followed by some unintelligible words and occasional laughter. Other patients in the waiting room are becoming visibly uncomfortable, so a nurse moves T.R. into an examining room. Later, as you attempt to examine her, she becomes very frightened. She whimpers and stiffens her body. Ten minutes later you realize that you are now behind schedule, and yet you still have not examined T.R.

Would it be fair to describe T.R. as an "unattractive" patient?

Generally, developmentally disabled patients are perceived as "unattractive." In understanding this label, we should first define the "attractive" patient as seen in the eyes of most clinicians. Attractive attributes include clear communication, cooperation during history and physical exam, good insurance, compliance, favorable response to treatment, and appreciation of the physician's efforts—as well as physical attractiveness. Attractive patients promise not to consume large amounts of physician time or staff resources on a given visit. Additionally, physically attractive people are often assumed to be more sincere, noble, and honest than unattractive people, and seem to have an easier time in life, whether in a job interview, in a criminal trial, or in the rain, waiting for a taxi.[8-11]

Conversely, so-called unattractive or "undesirable" patients are those who cause difficulty or frustration for the clinician. They may be repulsive for a number of reasons. They may represent a segment of society that is viewed as morally or socially "unfit" (i.e., addicts, prostitutes, the homeless). The unattractive patient may not be able to communicate clearly, may have a constellation of symptoms that perplexes the physician, or may be physically "unconventional" and thus unable to cooperate in the history or examination. Clinical encounters with them may feel unsatisfying to both doctor and patient.

After this difficult visit with you, T.R.'s mother complains to her friend, "As usual, the purpose of our visit was pushed aside, and the physician was more interested in her physical disability than in discussing other important topics like prevention and how we are coping." What went wrong in the clinician's office?

A complaint frequently voiced by caretakers and disabled patients is that physicians over-focus on their disability issues and forget their basic health needs. This may be a function of the short, "efficient" visits mandated by reimbursement agencies. It must be remembered that developmentally disabled patients require all of the same investigations that "unimpaired" patients require, or more. For example, a female disabled patient with abdominal pain requires routine evaluation as well as a pelvic exam with STD and pregnancy tests. There always exists the risk of sexual abuse, pregnancy, or infection. The disabled are by no means immune to the abuses experienced by members of society at large, and they may be more easily victimized.

Recently T.R. had a similar experience with a dentist. "He never got beyond her disability," her mother says. "He actually asked, 'Why would you want to do anything for her?'" What was behind the dentist's comment?

Health providers may have difficulty understanding the rationale for elective care for the disabled. Moreover, due to a variety of barriers (skill, knowledge, attitudes) when treating the developmentally disabled patients, "accidental" breaches in their care are common. Some examples follow:

1. A woman with cerebral palsy who died of inoperable cervical cancer after never having had a Pap smear or pelvic exam despite annual physicals recorded by her assigned primary physician.
2. A cognitively disabled man who died of complications of undiagnosed diabetes after never having had a blood or urine sugar test performed, again despite having had annual physicals with a primary physician.[12]
3. A patient with Down's syndrome who experienced severe tooth decay because of his parents' fear of dentists following a horrible experience with general anesthesia, as insisted upon by one dentist during a routine exam.

Such examples underscore the need to consider the routine health maintenance needs of the disabled, so often overshadowed or forgotten in the face of the obvious disability. In addition to presenting unique needs, disabled children and

adults need the same developmentally appropriate preventive care as other patients. They require immunizations, dental care, support and counseling, and vigilant emergency care. As they age, their bodies are not immune to myopia, heart disease, obesity, gynecological problems, and dental caries. Though it is more difficult to make diagnoses, prevalence of routine problems can be quite high in the developmentally disabled population. The presence of visual impairment in such patients, for example, has been found to be 10 times that of adults without developmental disability.[13]

How can physicians improve encounters with developmentally disabled patients?

Enhancing communication is the key. Clinicians can take these first steps to improve treatment for this population.

1. Introduce yourself to the patient with a friendly greeting and a handshake.
2. Listen carefully and give the patient or caretaker adequate time to speak. When evaluating patients with disabilities who have an acute problem and are unable to provide a history, it is essential to try to obtain information from people who know them. Sources are caregivers, instructors at schools or adult workshops, nurses or case managers, or even office staff familiar with the patient. Such people can be amazingly adept at "translating" the communication, verbal or otherwise, offered by the patient.
3. Maintain eye contact and talk with the patient, even if most of the conversation is directed toward the caretaker. Use touch when appropriate, and attune yourself to the patient's nonverbal behaviors and emotional displays. It is often possible to deduce a history by eliciting comparisons with past nonverbal behaviors. For example, one may learn that when patient "Susan" had a previous tooth infection, she was observed in difficult behaviors, and she is now repeating the behaviors.
4. Do not be embarrassed to ask for clarification when something is unclear.
5. Find out what is important to the patient and make sure you address those concerns.
6. Use the patient's or caretaker's words whenever possible. The best terms to use when speaking with the developmentally disabled are those that will facilitate understanding between doctor and patient and family. If a patient's family does not understand the term "cognitively challenged" but does understand "mentally retarded," then the latter would be better to use, even though "mentally retarded" is no longer considered a politically correct term.
7. Explain the course of events for the given visit and expectations for future visits. Involve home caregivers or home healthcare workers in treatment plans.
8. Acknowledge your understanding and limitations, and communicate your understanding to patients by saying something like, "That must be very difficult for you, and I'm sorry that I can't help with that particular problem."
9. Offer support and partnership by helping to connect patients with resources.

Table 2

Stepwise approach to a strategy for action with a difficult patient

Awareness
Establish self-awareness of distress (dread, diaphoresis, panic, etc.).
- "Something's wrong!"
- "I wish I weren't here!"
- "This person makes me feel uncomfortable."
- "I can't even look at this person."

Reflection
Be curious about what is happening, acknowledge your own emotional reactions, and attempt to label your feelings and understand and master your emotions.
- "How am I feeling?"
- "How are they feeling?"
- "What would I like to say to this person?"
- "What will I say?"

Assess problems by using your feelings as a diagnostic tool.
Ask yourself:
- "Is this discomfort caused by me?"
- "The patient's problem?"
- "The illness?"
- "All of the above?"

Decision
Accept or reject the challenge: "Do I choose to work with this patient or not?"
- If "no," what alternatives are available to you and the patient?
- If "yes," commit to working on relationship issues as well as medical issues.

Ask yourself, "Would it be helpful to discuss the problem with the patient or the caregiver?"

Solution
Foster communication with the patient or caregiver.
- "I find it difficult to proceed, knowing that you have a different view of the situation than I do."
- "Are we working together as well as we could?"

Acknowledge the patient's (or caregiver's) difficulty.
- "I sense you are angry (or annoyed) with me. May we discuss this together?"
- "This appears to be difficult for you to talk about. Is there some way that I can make it easier?"

Encourage problem solving (with patient, caregiver, or both).
- "I want to solve this problem we're having. My thoughts on the situation are _____. What are your thoughts?"

Collectively decide on your ideal role and where others can share in responsibility.
- "What were you hoping I would be able to do for you today?"
- "You've had quite a bit of experience with doctors. What works best with you?"
- "I am going to need to examine her ears. Are there suggestions you have for how I might do this without causing additional pain or worry?"

Explain what you can and cannot do for them.
- "I'd like to be your doctor. For me to be effective, though, I am going to need your help. Would you be willing to _____?"

Based on "Difficult physician-patient relationships," Bayer Institute for Health Care Communication; 1995.

T.R. and her mother prove to be extremely difficult and time-consuming. What strategies would you consider?

When behavioral interventions fail, it has been suggested that anticipated troubles can be alleviated by premedicating problematic patients with lorazepam 0.5mg PO 1 hour prior to an office visit,[7] but this procedure is no panacea when deeper conflicts with patients and caretakers are present. In these cases, physicians must first acknowledge there are problems. They must become aware that they are feeling uncomfortable; they must take time for reflection. Either implicitly or explicitly, they need to decide whether or not to make the commitment

to care for the disabled patient. Then they need to arrive at a solution to move forward. While reading through Table 2, visualize yourself in an awkward situation with a patient or person with whom you feel uncomfortable.

Ethical questions

If healthcare resources were unrestricted, any patient's or family's reasonable request for service could be honored, no matter what the cost. Transplant surgeries would be more common, and lives would be extended for short times at great expense. Unfortunately, resources are tightly restricted, and when costs are assessed against the benefits of individual medical treatments, costs often outweigh projected benefits. In the case of developmentally disabled patients, moreover, projected benefits of treatment can be even less tangible and thus become the subject of emotionally charged disputes. Many families of disabled patients have found physicians reluctant to perceive "real" benefits in nonemergent treatments aiming to improve a disabled person's lifestyle: eye surgeries, hearing treatments, orthodontic work. The issues are many.

What are some of the special considerations when determining competence and consent with developmentally disabled patients?

Informed consent requires, by definition, a mentally competent decision-maker. Yet in cases of cognitive disability, it may be difficult to determine competence. Legislation is not consistent among states with regard to consent issues when a patient may be, even at baseline, potentially incompetent for decision-making. In general, though, legislation tends to err toward patient autonomy, unless a judge has agreed to a conservatorship, wherein guardians are granted the legal right to make all medical decisions, or at least to have their side heard in court.

Even so, consistency is difficult. For example, some probate judges always refuse guardians' petitions for abortion or sterilization, whereas others in the same district are more liberal. In the United States, local regional centers—private nonprofit centers contracted by states to assist in residential, educational, social, and medical services for disabled people—are a good source for the names of lawyers who are experienced in legal issues of developmental disability.

Conclusions

Patients with developmental disabilities and their caretakers constitute a population unaccustomed to satisfactory treatment. Because of the difficulties they present (communication, coordination, cognition, fear, resistance) and added resources they require (time, referrals, ancillary staff), these patients and their caretakers can be frustrating for the clinician. Importantly, though, it is not the clinician's obligation to enjoy treating such patients; neither is it the patient's obligation to please the physician. Instead, the physician's obligation is to use strategies such as those described above to recognize, accept, and then restrain any negative feelings for the patient.[1] The ultimate aims are that medical judgment and professional decisions remain undistorted by personal insecurity or hostility, and that future encounters with developmentally disabled patients evolve toward greater satisfaction for patients, caretakers, and physicians.

We thank The Lanterman Regional Center for their help.

Table 3

Ethical issues in caring for the disabled

Personal worth
Do different people in society have different worths? If so, on what do you base the social worth of a person?

Equal care
Do all members of society deserve equal care? Do you feel that a severely impaired person should have the same rights to health care (surgery, ICU, etc.) as any other person?

Obligations
Do you, as a physician, feel an obligation to care for all patients who want to see you, or do you feel you have the right to pick and choose the patients you want to see? What happens to those whom you refuse?

Compromising care
Is it acceptable to compromise the care of a patient when we perceive that the care won't make much difference? For example, should public funds be used for surgical correction of an aesthetic malformation of the jaw of a severely developmentally disabled girl?

Sexual rights
Do you feel that cognitively disabled persons have a right to be sexually active if they so desire? Is sexual desire a higher function and thus not seen in cognitively impaired persons?

Consent
When a patient is impaired, who is responsible for informed consent? What happens when patients and caregivers disagree? For example, should patient or caregiver have the ultimate decision on terminating a pregnancy, if the patient is a mildly developmentally disabled woman pregnant by her boyfriend and would like to continue the pregnancy? Who should decide on sterilization?

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CLINICAL EVIDENCE

This article comes from Clinical Evidence, a new resource for clinicians, produced jointly by the BMJ Publishing Group and the American College of Physicians-American Society of Internal Medicine. Clinical Evidence is an extensively peer-reviewed publication that summarizes the best available evidence on the effects of common clinical interventions gleaned from thorough searches and appraisal of the world literature. The first issue is available in book form in the United Kingdom, with a United States version planned for publication in October. The second issue, updated and expanded to cover more topics and questions, will be published 6 months later. Please see the advertisement for more information or visit our web site at www.evidence.org.

Non-metastatic prostate cancer

Questions: What are the effects of treatment in men with clinically localized prostate cancer? In men who have received primary treatment and remain asymptomatic, should androgen deprivation be offered when raised concentrations of prostate specific antigen are detected? What are the effects of treatment in men with locally advanced prostate cancer?

INTERVENTIONS

Clinically localized prostate cancer

Unknown effectiveness
Watchful waiting
Radical prostatectomy
External beam radiation therapy
Brachytherapy
Cryosurgery
Androgen deprivation
Androgen deprivation in asymptomatic men with raised concentrations of prostate-specific antigen after early treatment

Locally advanced prostate cancer

Beneficial
Radiation plus androgen deprivation (improves survival compared with radiation therapy alone)

Likely to be beneficial
Androgen deprivation initiated at diagnosis

Unknown effectiveness
Radiation therapy alone

DEFINITION

Prostatic cancer can be staged according to two systems: the tumor, node, metastasis (TNM) classification system and the American urologic staging system (see box). Non-metastatic prostate cancer can be divided into clinically localized disease and advanced disease.

Summary points

In men with clinically localized disease

- The data we found do not provide clear evidence for the superiority of any one treatment, including androgen deprivation. Limited data from one randomized control trial (RCT) suggest, however, that radical prostatectomy may reduce recurrence compared with radiation treatment.
- We found limited data from RCTs suggesting that radical prostatectomy or external beam radiation therapy may not improve survival or reduce the risk of metastatic disease or the need for palliative treatment compared with watchful waiting.
- External beam radiation therapy, brachytherapy, and cryosurgery have not been compared with watchful waiting in RCTs.
- We found no RCTs addressing the question of whether androgen deprivation should be offered to asymptomatic men in whom raised concentrations of prostate-specific antigen are detected after primary treatment or during watchful waiting.

In men with locally advanced disease

- We found limited evidence from RCTs suggesting that androgen deprivation initiated at diagnosis improves survival and reduces the risk of major complications compared with treatment deferred until disease progression.
- A systematic review found that adding androgen deprivation to radiation treatment improves survival compared with treatment with radiation alone.
- We found no good evidence that radiation alone is beneficial for survival.

INCIDENCE AND PREVALENCE

Prostate cancer is the most common nondermatologic malignancy worldwide and the second leading cause of deaths from cancer in men in the United States.[1] It caused an estimated 184,500 new cases and 39,200 deaths in 1998.[2] For a 50-year-old man with a life expectancy of 25 years, the lifetime risk of microscopic prostate cancer is about 42%, the risk of clinically evident prostate cancer is 10%, and the risk of fatal prostate cancer is 3%.[3]

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Prostatic cancer staging systems

Tumor, node, metastasis (TNM) classification system

Tumor	
T0	Clinically unsuspected
T1	Clinically inapparent (not palpable or visible by imaging)
T2	Tumor confined within prostate
T3	Tumor outside capsule or extension into vesicle
T4	Tumor fixed to other tissue
Nodes	
N0	No evidence of involvement of regional nodes
N1	Involvement of regional node
Metastases	
M0	No evidence of distant metastases
M1	Evidence of distant metastases

American urologic staging system

Stage A	No palpable tumor
Stage B	Tumor confined to the prostate gland
Stage C	Extracapsular extension
Stage D	Metastatic prostate cancer
Stage D1	Pelvic lymph node metastases
Stage D2	Distant metastases

ETIOLOGY

Risk factors include age, family history of prostate cancer, black race, and, possibly, higher dietary fat intake.

PROGNOSIS

The chance that men with well to moderately differentiated, palpable, clinically localized prostate cancer will remain free of symptomatic progression is 70% at 5 years and 40% at 10 years.[4] The risk of symptomatic disease progression is higher in men with poorly differentiated prostate cancer.[5] Morbidity from local or regional disease progression includes hematuria, bladder obstruction, and lower extremity edema. Despite widespread testing for prostate-specific antigen and increased rates of radical prostatectomy and radiation therapy, population-based studies show that rates of death from prostate cancer in the United States have declined by only about 1/100,000 men since 1992.[6,7] Regions of the United States that have experienced the greatest decreases in mortality are those with the lowest rates of testing for prostate-specific antigen and treatment with radical prostatectomy or radiation.[7] Countries with low rates of testing and treatment do not consistently have higher age-adjusted rates of death from prostate cancer than countries with high rates of testing and treatment, such as the United States.

AIMS

To prevent premature death and disability while minimizing the adverse effects of treatment

OUTCOMES

Survival; time to progression; response in terms of symptoms and signs; quality of life; adverse effects of treatment

METHODS

We searched for systematic reviews and RCTs using the search strategy of the Department of Veterans Affairs Cochrane Review Group on Prostatic Diseases (Cochrane Library and MEDLINE to the end of 1998). We reviewed all systematic reviews and RCTs that were identified.

Question: What are the effects of treatment in men with clinically localized prostate cancer?

OPTION: WATCHFUL WAITING

We found no direct evidence from RCTs that watchful waiting improves the length or quality of life in men with clinically localized prostate cancer compared with other management strategies.

Benefits

We found two systematic reviews.[1,8] In men managed by watchful waiting, prospective cohort studies report 15-year disease-free survival of 80%, ranging from 95% for well-differentiated cancers to 30% for poorly differentiated cancers.[9,10]

Versus early androgen deprivation, we found no RCTs.

Versus radical prostatectomy, we found 1 RCT (see below).[11]

Harms

Expectant management does not remove a cancer that may progress and cause death or disability.

Comment

There is about a 10-year lead time between the detection of cancers by raised concentrations of prostate-specific antigen and detection by digital rectal examination or the development of symptoms. This means that outcomes are likely to be similar in men with palpable tumors who are followed for 15 years and men whose tumors are detected in raised concentrations of prostate-specific antigen who are followed for 25 years.

OPTION: RADICAL PROSTATECTOMY

Limited data from RCTs provide no evidence that radical prostatectomy improves outcome compared with watchful waiting. It may reduce the risk of metastases compared with external beam radiation therapy. Radical prostatectomy carries the risks of major surgery and of sexual and urinary dysfunction.

Benefits

We found two systematic reviews.[1, 8]

One RCT compared radical prostatectomy versus watchful waiting in 142 men with clinically localized prostate cancer. After a median follow-up of 23 years (range, 19-27 years), no difference in survival was detected between the two groups (median survival 10.6 years with prostatectomy versus 8 years with watchful waiting, no confidence interval quoted).[11]

One RCT compared radical prostatectomy versus external beam radiation in 97 evaluable men with clinically localized prostate cancer. Men receiving radiation treatment had an increased risk of metastases (4 "treatment failures" with prostatectomy versus 17 with radiation treatment).[12]

Harms

Fatal complications have been reported in 0.5% to 1% of men treated with radical prostatectomy and may exceed 2% in men aged 75 years and older.[13] Nearly 8% of men older than 65 years had major cardiopulmonary complications within 30 days of an operation. The incidence of other adverse effects of surgery was over 80% for sexual dysfunction, 30% for urinary incontinence requiring pads or clamps to control wetness, 18% for urethral stricture, 3% for total urinary incontinence, 5% for fecal incontinence, and 1% for bowel injury requiring surgical repair.[1, 14-16]

Comment

Both RCTs of radical prostatectomy were conducted before the advent of tests for prostate-specific antigen and were too small to exclude a clinically important difference between groups. Radical prostatectomy may benefit selected groups of men with localized prostate cancer, particularly younger men with higher-grade tumors. The available data suggest, however, that in most men the potential benefits in quality-adjusted life expectancy are small at best and sensitive to patients' preferences.[8] Studies have found no differences among groups treated with radical prostatectomy, radiation, or watchful waiting when evaluating general health-related quality of life.[17] Two ongoing trials are comparing radical prostatectomy versus watchful waiting.[18, 19]

OPTION: EXTERNAL BEAM RADIATION THERAPY

We found limited evidence from one small RCT that, compared with radical prostatectomy, external beam radiation therapy increases the risk of metastases in men with clinically localized prostate cancer. It has not been compared directly to watchful waiting.

Benefits

Versus watchful waiting, we found no RCTs.

Versus radical prostatectomy, we found one RCT.[12]

Harms

The RCT made no mention of adverse effects of treatment.[12] A survey of men treated with external beam radiation therapy reported that 7% wore pads to control wetness, between 23% and 32% of men were impotent, and 10% reported problems with bowel dysfunction.[20] Treatment-related mortality is <0.5%.[1] External beam radiation therapy requires that men return for daily outpatient treatment for up to 6 weeks.

Comment

Up to 30% of men with clinically localized prostate cancer treated with radiotherapy still have positive biopsies 2 to 3 years after treatment.[21] Up to 60% have biochemical evidence of recurrence, which may reflect either distant or local recurrence.[22, 23]

OPTION: BRACHYTHERAPY

We found no direct evidence from RCTs that brachytherapy improves the length or quality of life in men with clinically localized prostate cancer.

Benefits

We found no systematic reviews or RCTs.

Harms

Complication rates reported from case series include urinary retention (6%-7%), incontinence (1%-6%), cystitis/urethritis (4%-7%), proctitis (1%-12%), and impotence (6%-50%).[24] Long-term outcomes from a representative national sampling of men have not been reported.

OPTION: CRYOSURGERY

We found no direct evidence from RCTs that cryosurgery improves the length or quality of life in men with clinically localized prostate cancer.

Benefits

We found no systematic reviews or RCTs.

OPTION: ANDROGEN DEPRIVATION

We found no direct evidence from RCTs that androgen deprivation improves the length or quality of life in men with clinically localized prostate cancer.

Benefits

We found no systematic review or RCTs.

Harms

Adverse effects of androgen deprivation include osteoporosis, weight gain, hot flushes (10%-60%), loss of muscle mass, gynecomastia (5%-10%), impotence (10%-30%), and loss of libido (5%-30%).[25] These adverse effects are particularly

important when considering treatment in men with a long life expectancy or treatment duration, such as younger men with lower-grade cancers.

Comment

Treatment with androgen deprivation may help to relieve anxiety in men diagnosed with clinically localized prostate cancer by giving the sense that something is being done.

Question: In men who have received primary treatment and remain asymptomatic, should androgen deprivation be offered when raised concentrations of prostate-specific antigen are detected?

The effects of initiating androgen suppression when prostate-specific antigen rises or persists after primary treatment have not yet been evaluated in RCTs.

Benefits

We found no systematic reviews or RCTs.

Harms

Potential harms include unnecessary or inappropriate treatment.

Comment

Clinicians often monitor blood concentrations of prostate-specific antigen and offer androgen suppression when these rise. Consequently, more men with disease persistence are being considered for androgen suppression, and treatment is being initiated earlier in the natural course of the disease. RCTs are needed to evaluate the effectiveness of this approach and of intermittent treatment during which androgen suppression is initiated when concentrations of prostate-specific antigen rise after primary treatment and is discontinued when the antigen concentrations return to baseline.

Question: What are the effects of treatment in men with locally advanced prostate cancer?

OPTION: ANDROGEN DEPRIVATION

RCTs have found that in men with locally advanced disease androgen deprivation initiated at diagnosis reduces complications and may improve survival. Androgen deprivation improves survival in men with locally advanced disease treated with radiation.

Benefits

Versus no initial treatment, we found one systematic review that identified no recent RCTs. Three RCTs performed between 1960 and 1975 compared androgen deprivation (diethylstilbestrol, orchiectomy, or estrogens) versus no initial treatment in about 4000 men with all stages of prostate cancer. They found no difference in overall survival. Reanalysis of updated data from these RCTs provided tentative evidence of a modest survival advantage with androgen deprivation.[26]

Comparing immediate (initiated at diagnosis) versus deferred androgen deprivation, we found one systematic review that identified three RCTs (n=2143), two of which were conducted in the 1960s.[25] None had a uniform protocol for initiating deferred treatment, so deferred treatment in these trials reflects the varied practices of the treating clinicians. Meta-analysis found no significant survival difference at 5 years between immediate androgen deprivation compared with deferred androgen deprivation (hazard ratio 0.914, 95% confidence interval [CI] 0.81-1.03).[25] The more recent trial, which included 938 men with stage C (locally advanced) and D (asymptomatic metastatic) disease, reported a survival benefit from immediate treatment (62% of deaths were from prostate cancer compared with 71% in the deferred treatment arm, P<0.001). The survival benefit was limited to men with stage C disease.[27] Immediate androgen deprivation almost halved the risk of major complications, such as pathological fractures (absolute risk 2.3% vs 4.5% with deferred treatment), spinal cord compression (absolute risk 1.9% vs 4.9%), ureteric obstruction (absolute risk 7% vs 11.8%), and extraskeletal metastases (absolute risk 7.9% vs 11.8%). The report did not quote confidence intervals nor make clear the time interval over which outcomes were recorded, though this seemed to be at least 10 years. Again, the lower incidence of complications was more apparent in men presenting with stage C disease.

Radiation therapy plus androgen deprivation

We found one systematic review, which identified four RCTs comparing early versus deferred androgen deprivation in men receiving external beam radiation therapy. Early androgen deprivation was initiated at the same time as radiation treatment for locally advanced or asymptomatic clinically evident metastatic prostate cancer and continued until the development of hormone-refractory disease. The deferred group received radiation treatment alone, with androgen deprivation initiated only in those in whom the disease progressed.[25] Meta-analysis found a difference in overall 5-year survival in favor of early androgen deprivation compared with deferred deprivation (hazard ratio 0.63, 95% CI 0.48-0.83; percent surviving at 5 years 76.5% vs 68.2%, absolute risk reduction 8.3%; number needed to treat at 5 years = 12).[25]

Harms

Adverse events were not well reported in the RCTs. Earlier initiation of androgen deprivation means longer exposure to adverse effects, which include osteoporosis, weight gain, hot flushes (10%-60%), loss of muscle mass, gynecomastia (5%-10%), impotence (10%-30%), and

loss of libido (5%-30%).[25] These adverse effects are particularly important when considering treatment of men with a long life expectancy or younger men with lower-grade cancers.

Comment

The RCTs conducted in the 1960s[25] included men who were older and had more advanced cancers than those in the more recent RCT.[27] RCTs are needed to evaluate the effectiveness of neo-adjuvant androgen deprivation to downstage the tumor before surgery when disease extends beyond the capsule.

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PRACTICE POINT

Fancy drugs for worried folks

When Mrs. Boronowski, aged 67, went to Dr. Jingle for her nervous indigestion and multiple allergies, she left his office with a whole bunch of prescriptions. She was given omeprazole ($4 a tablet), even though belladonna or a bottle of amphojel would have done as well. To calm her shattered nerves she received buspirone ($1.30 a tablet), because diazepam is now too common to be effective. For her allergies, Dr. Jingle prescribed loratidine ($2.20 a tablet), because chlorpheniramine at 2¢ would have made her too sleepy to tolerate her tranquilizer; and he also gave her the newest hypnotic, zolpidem ($1.70 a tablet), highly recommended by the friendly detail man. She also takes atorvostatin ($3.60 a tablet), because dieting is so difficult; a multivitamin B tablet (for energy), yeast, ascorbic acid, vitamin E, and for her systolic hypertension, losartan ($1.30 a tablet)—why prescribe mere generic atenolol?

When Mrs. Boronowski returned home, she looked at the pharmacist's bill. She sent it to her insurance company and immediately felt better.

In the future, if President Clinton has his way, she will send her bill to Medicare, for being over 65, she would be entitled to such coverage. At present one third of Medicare recipients are reported to have no drug coverage. Mr. Clinton would like to remedy this by providing full coverage for everybody, including Mrs. Boronowski. This will probably become an election issue and a political football. The pharmacy industry fears that price controls will surely follow and argues that they will kill the golden research goose that has revolutionized modem therapeutics. Mrs. Boronowski's bill may indeed drop by 20%, but Dr. Jingle will continue to prescribe the newest and dearest drugs, and the taxpayer will foot the bill.

Meanwhile, down at the gas station, Mr. Suggs, who pumps gas for small wages, has a painful duodenal ulcer relieved only by omeprazole ($4 a tablet), which he has to pay for himself because he has no insurance. His neighbor has had a kidney transplant and cannot afford to buy his antirejection drugs. But another neighbor has a "nervous condition," a limp, takes cocaine, gets a bagful of free medicine from Medicaid each month, and watches soap operas most of the day.

I do not know if there ever was an ancient goddess of reason. But if there were, she assuredly remains perched high on Mount Olympus and has not yet descended among the mortals.

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MEDICINE CABINET

Drug treatment of depression

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Depression is an important mental health problem. Because it is often unrecognized or not properly treated, it causes distress, social impairment, and an increased risk of death for the individual, as well as generating large costs for society. Several efficient treatments and strategies exist, however, among which antidepressant drugs are the main option.

Methods

This article is based on a review of recent research on the use of antidepressant drugs in treating depression. Research papers and recent comprehensive reviews are cited.[1] In areas of uncertainty, we make suggestions based on personal experience.

General considerations

Most patients with major depression[2] (see box) are best treated with a combination of antidepressants and psychotherapy. Some patients with mild to moderate major depression may be helped by the provision of supportive care, problem-solving techniques, or specific psychotherapy, such as cognitive therapy alone. A patient's symptoms may seem to be a reaction to environmental factors alone, but that fact does not in itself preclude drug treatment.

Simplified diagnostic criteria for a major depressive episode

- Five or more of the following symptoms have been present nearly every day for 2 weeks; at least one of the symptoms is (a) or (b):
  - (a) Depressed mood most of the day
  - (b) Markedly diminished interest or pleasure in all or almost all activities most of the day
  - (c) Significant weight loss or weight gain or decrease or increase in appetite
  - (d) Insomnia or hypersomnia
  - (e) Psychomotor agitation or retardation
  - (f) Fatigue or loss of energy
  - (g) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional)
  - (h) Diminished ability to think or concentrate, or indecisiveness
  - (i) Recurrent thoughts of death, recurrent suicidal ideation, suicide attempt, or a specific plan for committing suicide.
- Symptoms cause clinically significant distress or impairment in important areas of functioning.
- Symptoms are not due to the direct psychological effects of a substance or a general medical condition.
- Symptoms are not better accounted for by bereavement.

Summary points

- In general, no antidepressant drug is clearly more effective than another.
- Outcome can be significantly improved by nonpharmacological factors, such as a good therapeutic alliance between the doctor and the patient.
- A practical approach is to prefer newer antidepressants in mildly and moderately depressed patients and tricyclic antidepressants in severely depressed patients.
- It usually takes 1 to 4 weeks of treatment with antidepressants before an effect is evident; this delay may be longer in elderly people.
- If patients do not respond to treatment, check compliance and reconsider the diagnosis before changing or adding drugs.
- After the initial treatment response, the drug should be continued at the same dose for at least 4 to 6 months.
- The dose should be gradually decreased over several weeks before withdrawal.

Therapeutic effect

About 60% of patients with major depression will respond to their initial drug treatment, regardless of the type of antidepressant used. Response is defined as a decrease of at least 50% in symptom ratings on a depression rating scale during the first 4 to 8 weeks of treatment.[3] Of the remaining 40% of patients, some respond partially, and some do not respond at all. It generally takes 1 to 4 weeks for an antidepressant to take effect.

In controlled trials, about 30% of patients respond to placebo. Thus, the overall clinical effect seems to be influenced by nonpharmacological factors. One important factor is the therapeutic alliance between the doctor and the patient.[4] The difference between drug and placebo effects increases as the severity of the depression increases. In milder forms of major depression, antidepressants may be no better than placebo, although patients with more chronic "low-grade" forms of depression, such as dysthymia, may benefit from antidepressants.[5,6]

The different types of antidepressant drugs are described in Table 1. Controversy exists about whether the newer antidepressants, particularly selective serotonin reuptake inhibitors, are as effective as tricyclic antidepressants. Several meta-analyses have recently compared the efficacy and tolerability of antidepressants. One meta-analysis found no differences in efficacy in inpatients or outpatients between selective serotonin reuptake inhibitors and tricyclic antidepressants.[7] Another suggested, however, that at least some tricyclic antidepressants may be more effective than selective serotonin reuptake inhibitors in inpatients, with the

strongest evidence for amitriptyline.[8] Moreover, well-conducted studies in severely depressed, hospitalized patients have indicated that clomipramine may be better than citalopram, paroxetine, and moclobemide.[9-11] Venlafaxine has been claimed to be more effective than selective serotonin reuptake inhibitors; this might be related, however, to the use of higher-than-standard doses.[12] Unambiguous evidence to support the claim of more rapid onset of action has not been obtained for any drug.

Adverse drug reactions

In general, differences in adverse reactions and toxicity are more important than the possible small differences in the clinical effects of various drugs. Tricyclic antidepressants cause peripheral anticholinergic effects such as dry mouth, constipation, and blurred vision, as well as central anticholinergic effects such as impaired concentration and confusion. Selective serotonin reuptake inhibitors predominantly cause nausea, diarrhea, anxiety, agitation, insomnia, and anorexia. In two recent meta-analyses, discontinuation rates due to adverse effects were generally higher in patients treated with tricyclic antidepressants than in patients treated with selective serotonin reuptake inhibitors.[7, 8] Long-term treatment with selective serotonin reuptake inhibitors can also cause sexual dysfunction, and patients affected by this may discontinue the drug.[13]

The adverse reactions associated with selective serotonin reuptake inhibitors also occur with other drugs that have a predominantly serotonergic profile, such as clomipramine, venlafaxine, and nefazodone, although nefazodone is less likely to cause insomnia and sexual dysfunction.[14] The limited data available suggest that only minor differences in adverse effects exist between the different selective serotonin reuptake inhibitors. The newer antidepressants are also occasionally implicated in more severe adverse reactions, such as seizures and hyponatremia. Some drugs have specific adverse effects, such as hypertension associated with venlafaxine and agranulocytosis with mianserin. An attempt to use clinical data to calculate the risk of a patient becoming manic as a result of treatment with antidepressants found that there was a rate of unipolar depression of less than 1% for placebo, tricyclic antidepressants, and selective serotonin reuptake inhibitors.[15]

The newer antidepressants are far less toxic than the older drugs. Of the tricyclic antidepressants, lofepramine has the lowest toxicity. There is no evidence that antidepressants are addictive.

Selecting a drug

When deciding which drug to prescribe, the context in which the drug is to be given is important. In general practice, most patients have mild to moderate depression and are probably less tolerant of adverse drug reactions.[16] In contrast, in severely depressed patients, a lack of effect is more important than the development of adverse effects. Thus a good approach is to prescribe newer, less toxic drugs for mildly and moderately depressed patients and to prescribe drugs acting on both serotonergic and noradrenergic neurotransmission, such as tricyclic antidepressants, in patients who are severely depressed. Among the newer drugs, there has been more experience with selective serotonin reuptake inhibitors.

Several specific conditions may, however, modify these general recommendations. The patient's response to drug treatment during previous depressive episodes is a valuable guide. Other important considerations are the adverse drug reactions experienced during previous treatment with antidepressants, concurrent somatic or other psychiatric diseases, and the use of other drugs that may interact with antidepressants.

Establishing the optimum dose

The delayed clinical response to antidepressants makes it difficult to establish the optimal dose quickly. The individual dose is usually decided by trial and error, with the patient's previous response being the most useful guide.

Tricyclic antidepressants have to be started at a low dose and increased gradually. Most selective serotonin reuptake inhibitors, however, can be administered at the recommended dose from the first day or after a few days of treatment at a lower dose. The doses of other, newer antidepressants can usually be increased more quickly than doses of tricyclic antidepressants. In primary care, patients commonly receive doses of tricyclic antidepressants that are lower than the recommended dose, whereas selective serotonin reuptake inhibitors are usually prescribed at the recommended dose.[17] This difference is probably caused by the different profiles of adverse reactions.

Table 1 *Classification of antidepressant drugs*

Type of antidepressant
Older antidepressants
*Tricyclic antidepressants**
Amitryptiline, amoxapine, clomipramine, desipramine, doxepin, imipramine, lofepramine, nortriptyline, protryptyline, trimipramine
*Other reuptake inhibitors**
Buproprion†, maprotiline, trazodone, viloxazine
Monoamine oxidase inhibitors (irreversible)
Isocarboxazid, phenelzine, tranlcypromine
Newer antidepressants
Selective serotonin reuptake inhibitors
Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Other reuptake inhibitors
Reboxetine‡, venlafaxine§
Monoamine oxidase inhibitors (reversible)
Moclobemide‖
Other antidepressants
Nefazodone¶, mianserin#, mirtazapine#

*Inhibits reuptake of serotonin or norepinephrine, or both. †Also inhibits reuptake of dopamine. ‡Inhibits reuptake of norepinephrine. §Inhibits reuptake of serotonin and norepinephrine. ‖Monoamine oxidase A inhibitor. ¶Inhibits reuptake of serotonin and blocks serotonin (5-HT2A) receptors. #Complex mechanism of action including presynaptic α_2 receptor blockade.

Reasons for consultation with or referral to a psychiatrist

- Uncertainty about diagnosis
- Severe depression, in particular with psychotic features or suicide risk
- Bipolar disorder
- Coexistence of other psychiatric disorders, such as alcoholism or severe personality disorder
- Failure to respond to treatment
- Intolerance of adverse effects

It is important to review patients' treatment regularly to check response, compliance, possible adverse drug reactions, and suicidal ideation. It has been suggested that the dose should be increased if patient compliance is good, yet there has been no response after 3 weeks. If there is a partial response, clinicians could wait another 2 weeks before increasing the dose.[18] For patients at risk of suicide, the amount of a drug prescribed in a single dose should be limited, particularly with the older, more toxic antidepressants.

The plasma concentrations of many antidepressants vary from 5- to 10-fold between patients given the same dose. This variability can mainly be explained by genetic differences in the metabolic capacity of hepatic cytochrome P-450 enzymes.[19] Therapeutic drug monitoring may therefore be helpful in establishing the optimum dose of these drugs and for investigating failures of treatment. The clinical value of routine monitoring has not been shown convincingly, however. Although concentration-effect relations have not been found for the newer antidepressants, drug monitoring might be justified in special cases, such as when low compliance or drug interactions are suspected.

Lack of response

When patients do not respond to the first-choice antidepressant at an adequate dose, compliance should be checked. If compliance is good, the diagnosis should be reconsidered and the patient should be investigated for the coexistence of another psychiatric disorder or a somatic or personality disorder. If further drug treatment is considered necessary, two strategies exist: the patient can be switched to a different antidepressant, or another antidepressant can be added to the existing regimen. There is little evidence to suggest which alternative is preferable. Many people believe that augmentation therapy should be handled by specialists.

If the decision is made to switch treatment, a drug with a different or broader mechanism of action should be chosen. Switching to a drug with an identical mechanism has been found to be effective in some cases, but the studies of this are not conclusive. It may be necessary for the patient to have a drug-free interval before starting the new treatment to avoid drug interactions. Irreversible and nonselective monoamine oxidase inhibitors should be used only in special cases, because of their potentially severe adverse effects.

The drugs most often added to antidepressant treatment are lithium, triiodothyronine, buspirone, pindolol, or, for patients receiving serotonin reuptake inhibitors, a compound acting on the noradrenergic system.[20] With the exception of lithium,[21] and to some extent triiodothyronine[22] and pindolol,[23] however, the evidence supporting augmentation is sparse. When antidepressant drugs are combined, the risk of drug interactions should always be taken into account. In certain situations, consultation with or referral to a psychiatrist should be considered (see box).

Length of treatment

Because the risk of relapse is higher during the first months after remission, treatment should generally be continued at the same dose for 4 to 6 months after the initial response to the drug.[24] The risk of relapse seems to be increased if there are residual symptoms[25] or if imminent or chronic life stresses exist. Longer treatment may therefore be warranted in such cases.

To avoid discontinuation reactions, treatment should be tapered down over several weeks before withdrawal. Although most of the focus has been on discontinuation reactions occurring during treatment with selective serotonin reuptake inhibitors, other antidepressants also cause such reactions.[26] Common discontinuation symptoms include dizziness, headache, paresthesias, nausea, anxiety, and irritability.[27]

Depression is recurrent in many patients. After the third, or in special cases the second, depressive episode, prophylactic treatment should be considered. For bipolar disorders, lithium or another mood-stabilizing drug is the treatment of choice, and referral to a psychiatrist is recommended. In unipolar depression, lithium and some antidepressants have been shown to reduce the risk of recurrence.[28] The length of prophylaxis has to be decided on a case-by-case basis. Some patients will benefit from treatment for long periods, or even for life. Although the doses required for prophylaxis are unclear, it is generally recommended that the dose to which the patient initially responded should be used.

Drug interactions

Several clinically important pharmacokinetic and pharmacodynamic drug interactions have been reported for antidepressants. The risk of drug interactions should therefore always be considered before treatment with an antidepressant is planned in combination with another drug. Antidepressants are metabolized by the hepatic cytochrome P-450 system.[19] Fluoxetine, fluvoxamine, and paroxetine, in particular, are potent inhibitors of cytochrome P-450 isoenzymes and may cause important pharmacokinetic drug interactions.[29] Serotonin reuptake inhibitors should not be combined with monoamine oxidase inhibitors because of the risk of the serotonin syndrome.[30] In

addition, a drug-free interval is usually needed when treatment switches between these two drug groups.

Pregnancy and lactation

Tricyclic antidepressants have been widely used during the first trimester of pregnancy and have not been shown to have any teratogenic effects. Moreover, several studies have concluded that fluoxetine does not increase the rate of malformations when used in the first trimester.[31, 32] Little or no information is available on the possible teratogenic effects of other, newer antidepressants with the exception of fluvoxamine, paroxetine, and sertraline.[33]

Neonatal adaptation disturbances have been reported after exposure to tricyclic antidepressants in the third trimester, and a recent study indicates that fluoxetine may also cause such symptoms.[31] Based on current knowledge, it is reasonable to assume that all antidepressants carry this risk. A study of preschool children suggested that exposure to antidepressants in utero does not adversely affect long-term neurodevelopment.[34]

With the exception of doxepin, maternal treatment with tricyclic antidepressants does not seem to harm breast-fed infants.[35] Although some concern has been expressed about use of fluoxetine while breastfeeding, no detrimental effects have been reported for other selective serotonin reuptake inhibitors, and the exposure of the infant to these drugs is lower than for fluoxetine. Little information is available, however, for most newer antidepressants.[35]

Treatment of elderly people

Elderly people are generally more susceptible to anticholinergic effects, so treatment with the newer antidepressants is preferred. If a tricyclic antidepressant must be used, drugs with pronounced anticholinergic effects, such as amitriptyline, should be avoided, and the dose should be lower than that given to younger patients. The antidepressant effect may be more delayed in elderly people than in younger patients, and treatment may need to be continued for longer than 6 months. Elderly people often take drugs for somatic disorders, and the risk of specific drug interactions should be taken into account.

Costs

Questions are being raised about whether the newer antidepressants are worth their considerably higher prices when compared with the tricyclic antidepressants. Studies have found an advantage for the newer antidepressants.[36] Most of these studies, however, used models and simulations based on estimations from clinical trials or meta-analyses rather than data from population studies. To answer these questions conclusively, health economic evaluations need to be carried out in long-term, naturalistic, prospective, and randomized studies of antidepressants in primary care.

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Why does air travel cause earache?

Martin Honeysett

When travelling in airplanes, people reach altitudes at which the total gas pressure is much lower than that at sea level. They must reduce middle ear pressure in order to equilibrate with the external pressure. The difference in pressure between the middle ear and the eustachian tube at high altitudes is large, even in pressurized aircraft. In this situation, pressure regulation usually takes place when the gas escapes from the middle ear through the eustachian tube to the nasopharynx.

Eustachian tube dysfunction is the major etiologic factor in the development of otitis media. When the airplane descends to sea level, the reverse occurs and pressure equalization takes place by the ventilation of the eustachian tube. In this case, the eustachian tube opens periodically and gas goes into the middle ear from the eustachian tube. Most of the patients who experience ear pain during flight develop this problem at descent rather than ascent because of the anatomy of the eustachian tube. The eustachian tube orifice on the nasopharyngeal side has elastic lips and can be closed up by the relatively high pressure in the nasopharynx.

For infants, drinking milk from a bottle during ascent and descent may aid in middle ear pressure regulation.

Infants and children may suffer from functional eustachian tube obstruction as a result of either decreased tubal stiffness or an inefficient active opening mechanism of the eustachian tube. They are at higher risk of developing middle ear disease during flight. In addition, patients who suffer from severe seasonal allergy or common colds, ciliary dysfunction, sinonasal disease, and immunodeficiency are at higher risk of developing otitis media during flight. Children with pressure equalization tubes can fly safely, because the pressure equalization in the middle ear takes place without relying on the function of the eustachian tube.

Most people are able to equilibrate this pressure difference with ease on descent or ascent. Some people may need to perform maneuvers to perform autoinflation, known as the Valsalva maneuver, a technique involving forced nasal expiration with the nose and lips closed. Small children may have difficulty performing this maneuver. For infants, drinking milk from a bottle during ascent and descent may aid in middle ear pressure regulation. When this maneuver fails, negative middle ear pressure may develop and can be painful. If the negative pressure in the middle ear is strong enough, serum transudate or blood may appear. This phenomenon is called barotrauma and can be easily diagnosed with an otoscope. You will see an effusion that may be hemorrhagic. In barotrauma, the actual negative pressure in the middle ear can be expected to exceed 60mm to 90 mm of water, the level at which middle ear transudate starts.

Serous otitis and hemotympanum can result in conductive hearing loss, up to 30 dB to 40 dB initially, and patients begin to have difficulty understanding faint speech. Usually the hemotympanum is self-limited and clears by the fourth to sixth week. Myringotomy is usually not recommended because this can introduce infection. If serous effusion is present, a trial of Medrol dose pack usually resolves the problem completely. If the patient has ruptured the tympanic membrane with barotrauma, I recommend the use of oral antibiotics.

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TOOLBOX

Sexual problems of disabled patients

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Many disabling conditions can produce sexual problems in men and women, including problems of desire, arousal, orgasm, or pain. Sexual difficulties may arise from direct trauma to the genital area (due to either accident or disease), damage to the nervous system (such as spinal cord injury), or as an indirect consequence of a disability. For example, cancer of any organ may not directly affect sexual abilities but can cause fatigue and reduce the desire or ability to engage in sexual activity. Similarly, psychological aspects of the disability, such as the dependence on others or one's own self-image, can profoundly disturb sexual arousal and function. The two main points for consideration are how disabling conditions affect sexual function and behavior and which sexual difficulties most commonly arise.

Effects of disability on sexual function

Women who undergo radical mastectomy or a disfiguring trauma often report concerns about their femininity and self-image, such as feelings of lowered self-worth or the fear that men will find them less attractive. Similarly, after disfiguring surgery, traumatic accidents, or experiences with erectile dysfunction, men often avoid intimacy and the opportunity to meet potential partners because of embarrassment. "Sexuality" encompasses the entire view of how people express what is sexual, a combination of all the physical, emotional, intellectual, and social factors that have influenced their development. A person who has either lost a body part or is not able to use a part of his or her body may still have sexual feelings, may still desire sexual relationships, and may still seek sexual stimulation. Defining sexuality more broadly than just its physical function is particularly important for people with disabilities.

Congenital disability

Congenital or birth impairments often affect all aspects of sexual development. Foremost is the lack of privacy and independence that accompanies both physical and cognitive disabilities. This problem can be particularly severe for disabled adolescents, who often miss out on normal sexual experiences. Cognitively impaired patients often receive little attention to help them explore issues of their sexual health. The patient (or parents or caregivers if the patient is unable) needs to be educated about both normal sexual development (menses, erections, etc.) and alterations that might result from the disability. Issues of masturbation, unwanted pregnancy, and sexual abuse need to be discussed in an open and value-free environment.

In contrast, acquired disabilities may have different implications. Impairments early in life can make people less confident sexually and reduce their expectations for what is open to them sexually in their relationships. Patients who become disabled in adulthood are much more aware of what has been lost. While the degree of adjustment to congenital and acquired disabilities may not be different, the process of adjustment can vary greatly. For example, men with cardiac difficulties such as angina often present with sexual problems because they are worried about bringing on an attack if they attempt lovemaking. Similarly, women with joint difficulties (such as rheumatoid arthritis and osteoporosis) may find sexual positioning painful and so avoid activity. In both cases, the patient may be extremely hesitant to bring up a discussion of sexual function, and may suffer unnecessarily.

Hidden impairment

Patients with an impairment that is hidden from others but which affects continence or sexual function often find the situation humiliating and avoid all social contact. For example, people with spina bifida and perineal paraplegia often walk without apparent difficulty, leading the public to be unaware of a disability. Despite their ability to be perceived as "normal," they experience problems with sexual functioning and with controlling their bladder and bowel. The unpredictability of control often leads them to avoid social mixing, intimacy, and sexual interactions, all of which increases their isolation. It is not uncommon for people with even relatively minor disabilities to present with a low self-confidence and a poor body image. Clinicians should take care not to confuse the severity of a disability with the severity of its impact on the patient (see Table 1).

Deteriorating conditions

In most cases of trauma, patients experience a loss that does not deteriorate, such as spinal cord injury or amputation. Some conditions, like multiple sclerosis, do deteriorate in either a stepwise or a gradual manner that requires mental adjustment to the initial diagnosis, and then constant reappraisal as the condition worsens. Sexual dysfunction may occur in multiple sclerosis initially as a direct result of demyelination of the nerve. It may also result through nonspecific indirect effects as the condition deteriorates or as a result of psychological effects stemming from poor self-image or from depression. There may be problems with other organ systems, as well

Detail from Boors carousing by David Teniers the younger, 1664

Patients with an impairment that is hidden from others but which affects continence or sexual function often find the situation unbearable.

Causes of erectile dysfunction

- Psychological factors are among the most common factors for erectile dysfunction
- Lesions in the anterior temporal lobe (vascular, traumatic, etc.)
- Complete suprasacral spinal cord lesion, which permits only reflexogenic erection
- Incomplete suprasacral spinal cord lesion, which allows erection of either reflexogenic or psychogenic origin
- Complete infrasacral spinal cord lesion, which abolishes erection
- Autonomic neuropathy leads to impotence (such as in diabetes)
- Radial pelvic surgery can cause damage to the local nerve plexus (such as abdomino-perineal resection of the rectum)
- Drugs that inhibit the action of acetylcholine
- Major vascular occlusion in the abdomen or pelvis, which impedes blood supply to penile tissue
- Fibrous plaques of Peyronie's disease and damage to the cavernosal tissue after prolonged priapism can be a major problem

as fatigue, anxiety, and altered desire in the patient's partner.

Healthcare providers caring for the disabled must address the sexual needs of the patients and their partners. The partner may not only have a reduced attraction to a disabled partner but also may have fears of hurting or otherwise making the partner uncomfortable. Issues of guilt, anxiety, and unfulfilled sexual desire may also be woven in with these concerns.

Ideally, conversations about sexual behaviors and feelings should take place with both the patient and the partner present, in order to clear up confusion and misunderstanding. The patient or the partner may prefer to discuss these issues in private, however, and it behooves the physician to open the door to such discussions.

Mental impairment

Some conditions, such as Huntington's chorea and traumatic brain injury, may alter a patient's ability to think in a reasoned way, and these conditions can affect sexual behavior. Injury to the reticular activating system of the pons and midbrain slows arousal, whereas injury to the frontal lobes may result in promiscuity because of reduced inhibition. Indirect effects of brain injury, such as alteration of endocrine function (for example, posttraumatic hypopituitarism), can also affect sexual drive and arousal.

People with learning difficulties often have problems developing an understanding of their sexual identity. This may be a direct consequence of their learning impairment or a result of overprotection by their families. Parents and caregivers often feel uncomfortable with a child's developing sexual behavior, possibly because of fear of exploitation or because of their own lack of understanding or acceptance of the child's sexual needs. The patient's primary care physician is often the person to whom family members first mention their worries, or the physician may be the first person to raise the issue. Unfortunately, the concept of anticipatory guidance—providing education about expected developmental milestones and anticipated problems—so common in pediatrics is rarely considered by caregivers of the developmentally disabled. Primary care providers should be familiar with common concerns about sexuality experienced by both disabled persons and their parents. Topics such as masturbation, pregnancy prevention/family planning, and sexual abuse certainly deserve discussion at the appropriate time.

Common sexual difficulties

Disabled persons may have never had a specific sexual experience (primary impairment) or may have become unable to continue with their sex life (secondary impairment). Primary functional impairments—such as a man's inability to get an erection or to ejaculate or a woman's pain, inability to allow penetration, or anorgasmia—are more common among patients with long-standing disabilities or those of early onset and are often hard to resolve. Men are more likely to present than women, possibly reflecting cultural perceptions of the importance of sexual performance and, now, the greater range of treatment options available (see Table 2).

Sexual function and arousal in men and women occur in response to reflexogenic genital stimulation or psychogenic desire in those with intact sexual drive mechanisms. Those with brain or spinal cord injury, or those whose injury or disease processes affect the spinal cord, experience partial or complete loss of sexual functions. They require comprehensive assessment of the level and degree of damage to the brain and nerve cord and the damage to upper and lower motor neurones (by testing the bulbocavernosal and anal wink reflexes). In neurological terms, male erection is similar to the female vasocongestive response and lubrication, while male ejaculation is similar to female contraction of the pelvic floor, perineum, and anal sphincter.

Erectile dysfunction

Loss of erectile function is the commonest sexual problem among disabled male patients. While the disabled may have a host of possible organic etiologies for erectile dysfunction, medication-related impairment is common and often easily corrected (see Figure 1). About 10% of commonly prescribed drugs produce erectile dysfunction.[1] These same drugs are used in disabled persons, and there is every reason to believe they have the same unintended side effects.

Even in cases of a clear physical cause, psychological factors are often also important. Physical loss of erection is most often treated by injection of drugs directly into the penis or, recently, with the oral drug sildenafil (viagra), which has been shown to enhance erectile ability in 70% to 90% of patients with spinal cord injuries, diabetes, and depression. Vacuum devices can be used by men who do not want to inject themselves, and there are topical preparations, but these are used less often because of their relative lack of success. Patients with erectile dysfunction of primarily psychological origin may benefit from a wide range of specialized psychological therapies, which usually include their partner.

Orgasm in women

The concept of orgasm had originally been considered to involve a reflexive pathway. Further research in this area led to the identification of a sensitive area women feel through the anterior wall of the vagina (the "G-spot") which, when stimulated, produces a fluid chemically different from urine and which in turn leads to the phenomenon of female ejaculation. It has been

Table 1

Key questions in cases of disability

Present condition
- Does the person have a congenital or acquired disability?
- Is the disability static or deteriorating?
- Is the disability observable by other people?

Effect of condition on sexuality
- Does the disability affect sexual function or sexuality?
- Does the disability impair cognitive or intellectual ability?
- Are there associated iatrogenic factors?
- Is fertility the principal concern?

Table 2 *Assessing sexual problems in disabled patients*

Mainly psychological cause of problem (Refer to psychosexual counseling)	Mainly organic cause of problem (Refer to suitable specialist)
Acute onset	Generally slower onset
Generally poor relationship with partner (refer for psychological counseling)	Good harmonious relationship with partner
Symptoms not consistent in all situations	Symptoms consistent in all situations and with all people
Major life events often present (births, deaths, potential or actual change in relationship, health, job)	Major life events rarely present
Coexisting problem with mental or physical health rarely common	Coexisting problem with mental or physical health present
Men with erectile dysfunction have nocturnal or early morning erections	No nocturnal or early morning erections in men with erectile dysfunction
Can respond to self-stimulation	No response to self-stimulation
Commonly aged ≤50 years	Commonly aged ≥50 years
Genitalia (including prostate) and secondary sexual characteristics seem normal	Genitalia and secondary sexual characteristics show abnormal structure or development
Normal results from investigations*	Abnormal results from investigations

*Complete blood count; blood urea and nitrogen (BUN); urinanalysis; liver function; and thyroxin, glucose, and sex hormone concentrations.

hypothesized that there are two different pathways involved in the sexual responses of women: clitoral stimulation provides arousal via the pudendal nerve and vaginal stimulation induces arousal via the hypogastric plexus and pelvic nerve.

Women with various complete neurological injuries to their spinal cords, however, often report the continuation of the experience of orgasm on vaginal stimulation. It has, therefore, been hypothesized that a third sensory pathway, the vagus nerve, which directly links the cervix to the brain and bypasses the spinal cord, enables orgasm in these women.

Difficulties with ejaculation

Ejaculatory dysfunction among disabled people is most common in men with spinal cord injury, multiple sclerosis, spina bifida, and transverse myelitis. Ejaculation involves closure of the bladder neck (through sympathetic stimulation) and relaxation of the external sphincter.

Patients with spinal damage often experience retrograde ejaculation into the bladder because of sympathetic damage, and various procedures have been used to induce an ejaculate for patients who want to have children. In men with an upper motor neurone lesion but with an intact sacral cord, vibratory stimulation is often used.

After training, vibratory stimulation of the penis can be attempted at home. Once the frequency and amplitude of the vibration have been selected, the vibrator is applied to the penis to stimulate the pudendal nerve.

If this is unsuccessful, patients with lower motor neurone injuries can be helped by electroejaculation. This involves the insertion of a stimulatory probe into the rectum to stimulate the midsacral roots directly, but it requires hospital attendance because of the complexity of the procedure and the potential side effects of pain and autonomic dysreflexia.

Fertility problems

For men with neurological impairment, obtaining semen with a reasonable sperm count and motility is a problem. The same difficulty occurs with many other injuries and as a side effect of drugs used to treat various conditions.

Women with traumatic brain injury, epilepsy, multiple sclerosis, and diabetes retain an anatomically intact reproductive system, but the physiological effects of their condition may alter ovulation or hormone secretion. The lower pregnancy rates reported in disabled women are probably the result of avoiding conception because of concerns over their ability to raise a family. It is important to assure that when the disabled person is cognitively intact, decisions about family planning, reproductive health, contraception, sexual orientation, and sexuality are made by that person, with all the attention to confidentiality and informed consent that would be offered to other sexually active persons. Those with congenital disorders known to affect fertility and childbirth should be given the opportunity to discuss any anxieties with a genetic counselor.

Assisted conception

Technology exists to obtain ejaculate from most men, but the problem of semen quality, particularly sperm motility, remains. The reason for this is unclear, although scrotal hyperthermia, long-term use of certain drugs, prolonged sitting in a wheelchair, and repeated urinary tract infections have all been suggested.

At the simplest level, couples can be taught how to obtain semen with a vibrator at home and introduce it into the vagina with a standard syringe. If sperm motility is low (<35%), in vitro fertilization can be useful. The process is also helpful for some men with spinal cord injury.

The recently developed techniques of micro-assisted fertilization require only small numbers of motile sperm. Intracytoplasmic sperm injection, in which semen is inserted directly into the egg cytoplasm, is more suited for those with low sperm counts.

Research indicates fertilization rates as high as 70% and childbirth rates as high as those with in vitro fertilization. Studies are currently assessing the effectiveness of using a small specimen of semen taken directly from the epididymis for in vitro fertilization or intracytoplasmic sperm injection.

Even in conditions of severe disability, such as tetraplegia, close monitoring by a team of specialists, including the spinal injury team and urological and gynecological services, should ensure maximum likelihood of conception and pregnancy. Options exist for improving sexual function and fertility for those with a wide range of disabling conditions. Such people do not wish for preferential treatment, but they do deserve equal opportunity and access to a fulfilling sex life.

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TOPIC IN REVIEW

Cirrhosis of liver

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DEFINITION

The term "cirrhosis" is derived from the Greek work *kirrhos,* meaning "tawny" and referring to the tan color of the liver. Cirrhosis is a histologic diagnosis, based on three essential criteria: diffuse disease, presence of fibrosis, and replacement of normal architecture by abnormal nodules. The initial step is deposition of fibrous tissue at sites of liver cell necrosis, which in the initial stages links portal and central areas or one portal/central area with another. As the disease advances, the fibrous bands become wider and denser, enclosing islands of hepatocytes. These islands, or nodules, are called "pseudolobules" because the normal lobular architecture is lost. Depending upon their size, the defect is termed as "macronodular" (>3 mm in diameter) or "micronodular cirrhosis." The histologic abnormality should involve the entire liver, since localized defects such as focal nodular hyperplasia do not constitute cirrhosis. It should be noted that while fibrosis is a reversible process, cirrhosis is not.

METHODS

The article essentially reflects my practice, amplified by reviews of the latest literature, culled from various sources.

EPIDEMIOLOGY AND PREVALENCE

The exact prevalence of cirrhosis is not known because the disease is often silent. Nearly 30% to 40% of cases are discovered at autopsy, indicating that in a substantial proportion of people, the disease goes undetected during life.[1] The number of deaths from cirrhosis in the United States varies from 12 to 15 per 100,000 population. The death rate dropped sharply to between 7 and 8 during Prohibition (1916-1932), but returned to the baseline after Prohibition laws were withdrawn.[2]

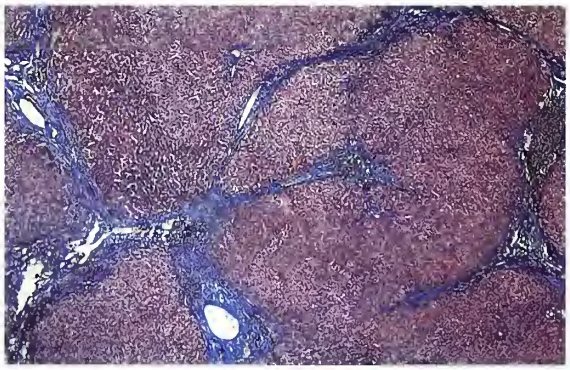

Figure 1 *Cirrhosis of liver. Broad fibrous bands are seen connecting portal tracts and central veins, resulting in the formation of pseudolobules (trichrome stain, x10).*

Summary Points

- The main challenge is to prevent progression to cirrhosis and then, in patients with cirrhosis, to minimize complications.
- Patients with abnormal liver tests should have a basic minimum diagnostic workup. Early diagnosis allows a chance for complete recovery in several diseases.
- Family physicians play a crucial role in prevention. Emphasis should be placed on avoidance of toxins (alcohol, drugs); use of safety measures against transmissible agents (HBV, HCV); and family screening for hereditary illnesses.
- Antiviral drugs have improved the outcome of HBV and HCV infections and should be used in all patients who qualify for this therapy.
- Complications such as variceal bleeding can be effectively controlled and prevented by endoscopic and drug therapies.
- Liver transplantation is the only definitive treatment for end-stage liver disease. Patients should be referred to a specialist before irreversible complications set in.

CLASSIFICATION

Several classifications have been devised, including morphological (macronodular and micronodular); histologic (posthepatitic, postnecrotic); etiological (viral, alcoholic); and clinical (compensated or decompensated cirrhosis). From a practical viewpoint, the most useful classification incorporates the latter two categories. Thus a complete diagnosis should state the cause of liver disease (e.g., alcoholic cirrhosis) and whether or not the patient has decompensated liver disease.

ETIOLOGY AND DIAGNOSIS

The causes of cirrhosis can be divided into three broad groups: hepatocellular, cholestatic, and hepatic venous outflow obstruction (see Table 1). The diagnostic and therapeutic approaches to these conditions are entirely different.

Laboratory investigations

Laboratory tests are performed to determine the presence and severity of the liver disease and to establish the etiology.

Liver tests

A predominant increase in serum aminotransferases (ALT and AST) suggests a "hepatitic" or hepatocellular disease, while a predominant increase in alkaline phosphatase indicates "cholestatic" or biliary tract abnormality. The ratio of serum AST to ALT and the level of enzyme elevation also provide useful informa-

Table 1 *Classification of cirrhosis according to etiology*

Hepatocellular	Cholestatic	Venous outflow obstruction
Viral hepatitis (B,C,D)	Biliary obstruction	Veno-occlusive disease
Alcohol	Primary biliary cirrhosis	Budd-Chiari syndrome
Autoimmune	Primary sclerosing cholangitis	Congestive heart failure
Metabolic	Drugs/toxins	Constrictive pericarditis
Steatohepatitis		Drugs/toxins
Drugs/toxins		

Drugs and toxins can cause all 3 forms of liver disease.

Table 2 *Diagnostic tests in chronic liver disease*

Hepatitic liver disease	Cholestatic liver disease	Outflow obstruction
Viral serology (HBV, HCV)	Blood tests	Imaging studies
Autoimmune (ANA, ASMA)	GGT, 5'NT, AMA	Doppler ultrasound
Hemochromatosis (iron saturation)	Imaging studies	MRI
Wilson's (ceruloplasmin, urine Cu)	Ultrasound, CT Scan, MRC	Portal/IVC venography
A1-AT deficiency (serum A1-AT)	ERCP	Cardiac catheterization
Drug and alcohol screen	Drug screen	Drug screen
Liver biopsy	Liver biopsy	Liver biopsy

ANA = antinuclear antibody; ASMA = anti–smooth muscle antibody; GGT = gamma glutamyl transpeptidase; 5'NT = 5' nucleotidase; AMA = antimitochondrial antibody; MRC = magnetic resonance cholangiogram; IVC = inferior vena cava.

tion. In hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, ALT is greater than AST; while in alcoholic liver disease, AST is greater than ALT. Serum ALT values rarely exceed 500 U/L in alcoholic liver disease; while in viral hepatitis, ALT values are often greater than 1000 U/L. The extent of enzyme elevation has no prognostic significance. Indeed, enzyme levels are often normal in cirrhosis. By contrast, abnormalities of serum albumin and prothrombin time indicate severe disease and carry a poor prognosis.

Tests to determine etiology

The type of workup is based on whether there is a hepatitic or cholestatic abnormality (Table 2). Because alkaline phosphatase is released from several organs (e.g., placenta, bone, GI tract), tests more specific for liver disease, such as gamma glutamyl transpeptidase (GGT) and 5' nucleotidase (5'NT), are performed whenever there is doubt about the diagnosis. In all forms of liver disease, liver biopsy helps to establish the diagnosis, severity, and prognosis of the disease and aids in the decision regarding use of antiviral therapy. Diagnostic tests for specific liver diseases are described under individual headings.

CLINICAL FEATURES

General

Patients with chronic liver disease and cirrhosis present in several ways.

Asymptomatic

Some patients are completely asymptomatic and the diagnosis is made incidentally on a routine blood test. These individuals may lead a normal life and die of an unrelated cause.

Vague ill health

Patients with cirrhosis, like those with other chronic disorders, often have vague symptoms such as fatigue, malaise, reduced libido, anorexia, nausea, and weight loss.

Decompensated liver disease

Advanced liver disease is indicated by the development of edema, ascites, easy bruising, and poor concentration and memory. These patients are prone to complications such as spontaneous bacterial peritonitis, portal hypertension (variceal hemorrhage), encephalopathy, hepatorenal syndrome, and liver cancer.

Physical signs

The typical physical findings are shown in Table 3. Patients with cirrhosis have a hyperdynamic circulation with tachycardia, a bounding pulse, and warm extremities. An interesting finding is the presence of orthodeoxia, or increased breathlessness (with decrease in PaO_2) in sitting or standing position but not while lying down. This defect is due to shunting of blood through collateral vessels, which are present in greater numbers in the lower lobes of the lungs. Signs of early encephalopathy should be investigated, including poor recall, inability to draw

Table 3 *Typical clinical signs in patients with cirrhosis*

Vitals	Extremities	Skin	Endocrine	Abdomen	CNS
Tachycardia	Clubbing	Petechiae	Gynecomastia	Ascites	Asterixis
↑Pulse pressure	Edema	Purpura	Testicular atrophy	Collaterales	↑Planters*
Orthodeoxia**	Ecchymosis	Hair loss	Amenorrhea	Big spleen	
Low-grade temp		Spiders		Nodular liver	
Palmar erythema				—	

* ↑Planters = upgoing planters; **orthodeoxia = decrease in PaO_2 (with shortness of breath) when patient changes from supine to standing position.

diagrams such as a star or a rectangle, and worsening handwriting. Unprovoked deterioration should prompt the search for complications such as infections, internal bleeding, renal failure, electrolyte imbalance (overenthusiastic diuresis), and hepatocellular cancer.

Associated abnormalities

Several liver diseases are associated with specific abnormalities. Patients with viral hepatitis may develop vasculitis and cryoglobulinemia (causing glomerulonephritis, peripheral neuropathy, etc.). Autoimmune hepatitis is associated with other autoimmune abnormalities. Several organ systems are involved in metabolic liver disorders.

COMPLICATIONS AND MANAGEMENT

Diet

There are no dietary restrictions in uncomplicated cirrhosis. Salt restriction is recommended once edema occurs, because patients with cirrhosis have a diminished ability to excrete sodium. Proteins are restricted only in the presence of hepatic encephalopathy.

Ascites and edema

Salt intake is restricted to 2g (88 mmol)/day. The diuretic of choice is spironolactone (Aldactone), which is combined with furosemide (Lasix) when rapid response is required. The starting dose is 100 mg spironolactone and 40 mg furosemide.[3] Weight loss should be 1 lb/day in the absence of edema, but there are no restrictions in presence of anasarca. If weight loss is suboptimal, 24-hr urine Na should be checked. A value >78 mmol/day indicates poor compliance with salt restriction. If urine Na is <20 mmol/day, the dose of diuretics should be increased by increments of 100 mg spironolactone and 40 mg furosemide to a maximum of 400 mg spironolactone and 160 mg furosemide. A third diuretic should not be added because of risk of electrolyte disturbances. Patients not responding to these measures, including more stringent salt restriction of 1g (44 mmol/day) or even 0.5 g/day (22 mmol/day), have "resistant ascites" and are candidates for liver transplantation. In the interim, large-volume paracentesis should be performed. Alternatively, peritoneo-venous shunts (LeVeen shunt, Denver shunt) may be used. Recently, transjugular intrahepatic portosystemic shunts have been employed with good results, but this indication is experimental.[4]

Spontaneous bacterial peritonitis

Patients who have cirrhosis with ascites are prone to bacterial peritonitis without a precipitating cause such as bowel perforation or intra-abdominal inflammation (diverticulitis, cholecystitis, etc.). Spontaneous bacterial peritonitis is suspected in the presence of fever, unexplained deterioration, and abdominal pain or tenderness.[5] The diagnosis is confirmed if ascitic fluid neutrophil count is >250/mm^3. The drug of choice is cefotaxime (Claforan), 1g qid for 2 weeks. Aminoquinolones (Norfloxacin, Ciprofloxacin) are also very effective.

Portal hypertension

Portal hypertension is a major complication of cirrhosis.[6] One third of patients with cirrhosis who have varices experience variceal bleeding within 2 years of diagnosis. Those who bleed have a 70% risk of rebleeding and a 30% to 50% risk of death. Acute variceal bleeding is treated with combined endoscopic (variceal sclerotherapy or banding) and drug therapy (somatostatin 50 ug/hr by continuous infusion for 5 days). Patients who continue to bleed are considered for transjugular intrahepatic portosystemic shunt or shunt surgery.[7] Since the rebleeding rate is high, some form of prophylaxis should be used, either endoscopic or drug therapy (nonselective betablockers: propranolol or nadolol) to reduce the portal pressure. Beta-blocker therapy is also useful in patients with large varices who have never experienced variceal bleeding.[8] Another complication of portal hypertension is splenomegaly and hypersplenism, which contribute to the leukopenia and thrombocytopenia in cirrhosis.

Encephalopathy

Chronic hepatic encephalopathy is characterized by mental slowing, somnolence, memory loss, flapping tremors (asterixis), and, in the late stages, coma. Treatment consists of a low-protein diet (40 g/day) and

lactulose in a dose sufficient to produce three to four bowel movements a day.[9]

Hepatorenal syndrome

Hepatorenal syndrome is defined as oliguric renal failure in patients with advanced liver disease. Typically, the urine has low Na content (<10 mEq/l). The syndrome is caused by reduced renal perfusion and glomerular filtration and is associated with a poor prognosis. There is no structural damage to the kidneys, and the syndrome is completely reversed if hepatic function is restored, such as after liver transplantation. Recently, some success has been obtained with the transjugular intrahepatic portosystemic shunt procedure.[10]

Hepatocellular carcinoma

Cirrhosis is a premalignant condition and is associated with an enhanced risk of hepatocellular cancer. Over the past two decades, the incidence of this type of cancer has increased in the United States, mainly because of the spread of HBV and HCV.[11] Preventive measures include screening with alpha-fetoprotein and ultrasonography every 6 months.

SPECIFIC LIVER DISEASES

Hepatocellular liver diseases

Viral hepatitis

Virus infections constitute the single most frequent cause of cirrhosis. Only HBV or HCV results in chronic liver disease. Hepatitis D virus is an incomplete virus that is pathogenic only in the presence of HBV. Viruses A and E cause a self-limited hepatitis that does not progress to cirrhosis. The newly identified hepatitis G virus does not produce any liver disease. HBV infection is diagnosed by the presence of hepatitis B surface antigen (HBsAg); HCV, by anti-HCV and HCV-RNA. Interferon was the first drug approved for treatment of viral hepatitis, and several preparations are in use: interferon alfa 2a (Roferon), alfa 2b (Intron), and consensus interferon (Infergen). These preparations have similar virus eradication rates and side-effect profiles. Most patients experience flulike symptoms, leukopenia, and thrombocytopenia. Less frequently, hair loss, irritability, depression, and thyroid dysfunction are seen. All adverse effects (except thyroid dysfunction) disappear when treatment stops.

Hepatitis B virus

The recommended dose of interferon is five million units daily for 16 weeks. Complete virus eradication is achieved in 20% of patients.[12] Lamivudine (Epivir), a nucleoside analogue, was recently approved for HBV.[13, 14] The response rate is similar to interferon, but lamivudine is easier to use (one 100-mg tablet/day) and is virtually free of side effects.

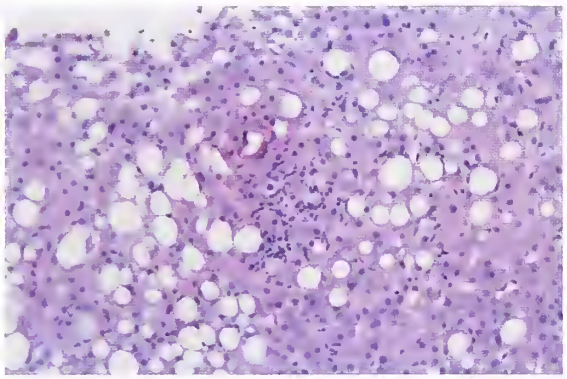

Figure 2 *Diffuse fatty liver in a chronic alcoholic; practically every hepatocyte is filled with fat (H&E stain, x10).*

Hepatitis C virus

Interferon is given in a dose of 3 million units 3 times a week for 12 to 18 months.[15-17] The virus eradication rate is 10% to 20%. In 1998 ribavirin, a guanosine analog, was approved for HCV. The combination of ribavirin and interferon results in virus eradication rates of 40%.

Vaccination

Very effective and safe vaccines are available against HAV and HBV.[18] The current recommendation is for universal vaccination against HBV, whereas HAV vaccine is used only in high-risk individuals: (1) subjects living in closed environments (such as day-care centers or institutions for the mentally or physically handicapped), homosexual men, and illicit drug users; (2) travelers to endemic areas, who receive a first dose at least 4 weeks before departure; and (3) patients with chronic liver disease.

Alcoholic liver disease

Heavy alcohol use over a prolonged time period (>5 years) may result in liver damage.[19] The critical dose

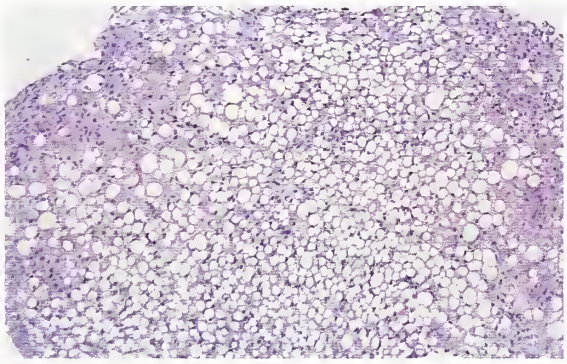

Figure 3 *Steatohepatitis. There is fatty change of the gepatocytes along with acute inflammatory cells in the center of the field (H&E, x20).*

is variable, but quantities greater than 60 g/day (four to five drinks/day, with a drink equal to one can of beer, one shot of liquor, or one glass of wine) are harmful. Only 10% of alcoholics develop liver disease. Women acquire the disease at lower dose and duration. There appears to be a genetic predisposition to alcoholic liver disease. The only effective treatment is complete abstinence. Patients with early disease (alcoholic steatosis) may recover completely. Acute alcoholic hepatitis is a serious illness that may progress despite abstinence. Treatment consists of a nutritious diet containing 1g/kg proteins (reduced to 40 g/day in presence of encephalopathy) and 2000 to 3000 calories, thiamine (100 mg), phosphorus, and magnesium. There is some evidence that prednisone (40 mg/day) is beneficial, but this treatment is controversial.

Autoimmune hepatitis

Autoimmune hepatitis occurs more frequently in women and is often associated with other autoimmune disorders such as thyroiditis, polyarthritis, polymyositis, hemolytic anemia, and glomerulonephritis. Physical signs include striae, Cushingoid features, and acne. Diagnosis is made by the presence of antinuclear and antismooth muscle antibodies and by liver biopsy. Prednisone is started at a dose of 20 to 40 mg/day, tapered off when liver tests become normal. Long-term immune suppression with azathioprine alone or with prednisone is usually required. Disease recurrences are treated with further courses of steroids.

Metabolic liver diseases

This is a group of genetic disorders, all with an autosomal recessive inheritance.

Hemochromatosis

This is the most common inherited disease of white people in the United States, affecting 1:200 to 1:400.[20] There is increased iron deposition in several organs, secondary to enhanced absorption from the bowel. The hemochromatosis gene (termed HFE gene) is seen in 85% of patients and contains a single point mutation (C282Y; cystine to tyrosine). The diagnosis is made by high iron saturation (>50% in women, >60% in men) and confirmed by liver biopsy. In addition to liver damage, there is abnormality of other organs, such as arthritis, heart failure, testicular damage, and bronzed skin. If diagnosed in time, hemochromatosis is completely treatable. Iron is removed by weekly phlebotomies until serum ferritin is <50 ng/ml and iron saturation is <50%, followed by maintenance treatment every 4 weeks. Family members are screened by serum ferritin and iron saturation values.

Wilson's disease

This disease is characterized by excess copper accumulation resulting in abnormalities of the liver, nervous system (tremors, incoordination, spasticity, seizures), arthralgia, renal tubular acidosis, hemolytic anemia, and cataracts.[21] Patients have low serum ceruloplasmin and elevated urinary copper. Treatment consists of chelation therapy with D-penicillamine or Trientrine. Patients are also given oral zinc (50 mg/day) to reduce copper absorption. The disease is curable if diagnosed in time.

A1-AT

Alpha-1 antitrypsin (A1-AT) deficiency inhibits the activity of trypsin and other proteolytic enzymes. In addition to liver damage, A1-AT patients develop emphysema, pancreatic fibrosis, and glomerulonephritis. Liver transplantation is the only treatment for this liver disease.[22]

Nonalcoholic steatohepatitis

Nonalcoholic steatohepatits is increasingly recognized as an important cause of chronic liver disease and cirrhosis. The characteristic histologic abnormality is steatosis (fat in hepatocytes) accompanied with inflammatory cells in nonalcoholic subjects. Diagnosis is made by liver biopsy. Treatment is limited to correction of any associated metabolic abnormalities (obesity, diabetes).[23]

Cholestatic liver diseases

Long-standing biliary obstruction of any etiology results in progressive liver disease and cirrhosis. A common feature is severe pruritus, often accompanied with skin excoriations.

Secondary biliary cirrhosis

This condition is seen with persistent obstruction of the bile ducts due to causes such as gallstones, strictures, and parasitic infestation.

Primary biliary cirrhosis

This is a disease of unknown etiology characterized by damage to the tiny intrahepatic bile ducts.[24] There is a 9:1 female predominance. Patients have hyperpigmentation, steatorrhea, xanthelasmas, and features of associated illnesses like scleroderma, CREST (calcinosis, Raynaud's disease, esophageal dysmotility, sclerodectly, telangiectasia) syndrome, and Sjogren's disease. Diagnosis is made by presence of antimitochondrial antibodies and liver biopsy. Ursodeoxycholic acid is the single most important treatment, improving all aspects of the disease: symptoms, liver tests, liver histology, and survival. Patients are encouraged to lead an active life and maintain good nutrition. Fat-soluble vitamins and calcium supplements are

required, especially for prevention of bone disease (osteoporosis). Treatment for pruritus is cholestyramine; other useful drugs are rifampin and naloxone (opiate antagonist).

Primary sclerosing cholangitis

Patients have fibrotic strictures of the extra- and intrahepatic bile ducts.[25] The most useful diagnostic test is endoscopic retrograde cholangiopancreatography. Associated illnesses are ulcerative colitis (seen in 75% of patients) and cholangiocarcinoma (seen in 15%). No specific medication is of benefit. Ursoedeoxycholic acid improves liver tests but does not alter the outcome. The treatment of pruritus and nutritional management are similar to primary biliary cirrhosis. Endoscopic dilatation is performed if a dominant stricture is present.

Venous outflow obstruction

Obstruction of the tiny intrahepatic veins is termed as veno-occlusive disease, seen after bone marrow transplantation (graft-to-host reaction), use of cytotoxic drugs, radiation to the liver, and consumption of Jamaican bush tea, which contains noxious pyrrolizidine alkaloids. Obstruction of the hepatic veins or of the adjacent inferior vena cava, called Budd-Chiari syndrome, is due to congenital webs or thrombosis of the vessels. Functional venous obstruction may occur in severe congestive heart failure and constrictive pericarditis, which, if not corrected, results in progressive liver failure and cirrhosis. Treatment is directed at removing the vascular obstruction or creating a surgical shunt to decompress the congested liver. Recently, good results have been obtained with the transjugular intrahepatic portosystemic shunt procedure.[26]

Drug-induced liver disease

Drugs and toxins cause a variety of liver abnormalities, including hepatocellular damage (isoniazid, methyldopa, amiodarone, and methotrexate); cholestatic liver disease (phenothiazine, estrogen, and anabolic steroids); and veno-occlusive disease (anticancer drugs).

LIVER TRANSPLANTATION

Since 1963, when the first transplant was performed, the status of liver transplantation has evolved from an experimental therapy to a life-saving procedure. The current survival rate after transplantation at 1 year and 5 years is 85% and 70%,[27] compared with 60% and 20%, respectively, after conservative treatment.[28] Liver transplantation is the definitive treatment for patients with decompensated liver disease (encephalopathy, coagulopathy, hypoalbuminemia) or a major complication (variceal bleeding).

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Med.Pix

A 4-year-old girl with a rash and joint pain

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QUESTION: A 4-year-old girl is brought to the doctor because of a rash and joint pain. Nine days earlier, the patient was seen for an upper respiratory infection and was given trimethoprim/sulfamethoxazole for presumed sinusitis. Two days prior to the visit, the mother called the on-call physician and explained that her daughter was developing a rash. The trimethoprim/sulfamethoxazole was stopped and the following night the child developed pain and swelling in her ankles, wrists, and hands. The child complained that her legs hurt and that it hurt her to walk. She had no abdominal pain.

In the office, the physical exam revealed the lesions seen in Figures 1 to 4. The young girl had an obvious rash on her face but did not appear toxic. She was communicative and friendly. She walked with some discomfort. She had a low-grade temperature of 37.7°C. Further exam revealed a rash on her trunk, buttocks, arms, legs, and feet. The primary morphology showed urticarial wheals and some target lesions (Figures 2 and 3). Swelling of both ankles with a purple discoloration was suggestive of purpura (Figure 4). Some swelling of the wrists and hands was also noted. The remainder of the physical exam was normal. Urinalysis showed trace protein and no blood.

What is the diagnosis and treatment for this condition?

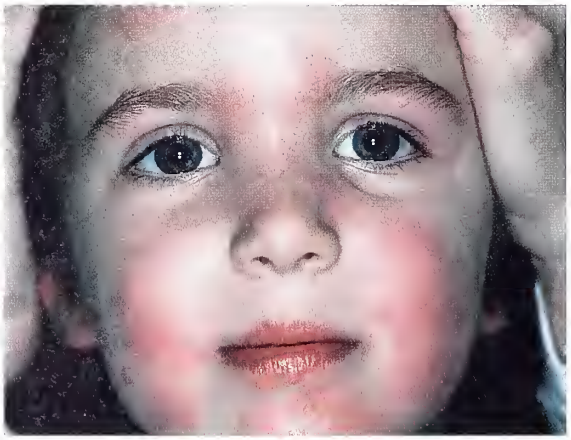

Figure 1 *Face*

Figure 2 *Flank*

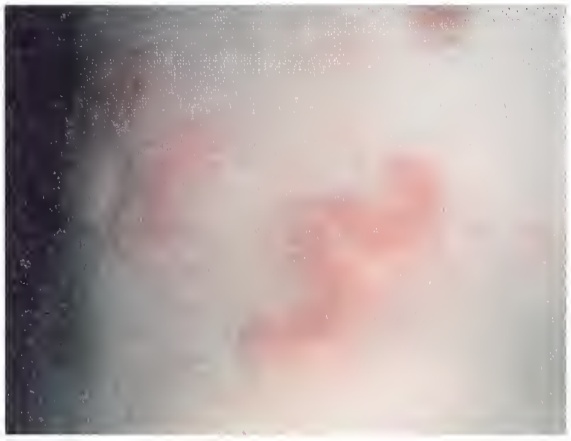

Figure 3 *Front*

Figure 4 *Ankles*

ANSWER: This young girl has Henoch-Schonlein purpura. Henoch-Schonlein purpura is characterized by a triad of palpable purpura, abdominal pain or renal involvement, and arthritis. This patient had the classic urticarial wheals and palpable purpura. Target lesions may also be seen in Henoch-Schonlein purpura. The patient had joint involvement with painful and swollen ankles and wrists. The ankles and knees are most frequently affected.[1] In this case, the patient did not have abdominal pain. Up to 65% of patients have colicky abdominal pain that may be severe and associated with vomiting.[1]

Renal involvement is the most serious sequela of Henoch-Schonlein purpura; hematuria is the most common manifestation of this renal involvement. Ten to 50 percent of patients may exhibit renal involvement and 1% may go on to chronic renal failure.[2] Our young patient had no hematuria and the trace proteinuria was not significant.

Henoch-Schonlein purpura is an autoimmune hypersensitivity vasculitis that occurs with a peak incidence at 4 years of age. The typical age range is 2 to 11 years of age, but Henoch-Schonlein purpura may occur in adults. Henoch-Schonlein purpura is seen in association with group A streptococci, mycoplasma, food reactions, insect bites, and drug allergies.[1] The American College of Rheumatology criteria for Henoch-Schonlein purpura are: age less than or equal to 20 years at disease onset, palpable purpura, acute abdominal pain, and biopsy showing granulocytes in the walls of small arterioles or venules.[3] The presence of two or more of these criteria allows the clinician to distinguish Henoch-Schonlein purpura from other forms of vasculitis with a sensitivity of 89% and a specificity of 88%. Our patient met two of these criteria and a biopsy was not necessary in the diagnosis or management of this case.

Treatment

The patient was treated with ibuprofen suspension; oral corticosteroids are generally not given unless abdominal symptoms are severe.[1] Three days later, our patient was no longer complaining of leg pain and was able to walk without any limping. The rash was resolving and the child was happy and playful. She was eating well and never developed any gastrointestinal symptoms.

Figure 5 *Lesions resolving*

Figure 5 shows the smiling face of our patient with the rash 90% resolved. A repeat urinalysis showed no blood and only trace protein. Two weeks later, a final urinalysis was normal. The rash and joint symptoms resolved completely.

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California's mandatory reporting of domestic violence injuries: does the law go too far or not far enough?

Contributions from Heidi Bauer, Donna Mooney, Hillary Larkin, Nancy O'Malley, Dean Schillinger, Ariella Hyman, and Michael A. Rodriguez

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What the law says

It is estimated that adult domestic violence affects 2 to 6 million intimate and married relationships each year in the United States.[1] According to the US Department of Justice, almost 1 million women are assaulted by intimate partners every year, and over half of these assaults result in injury.[2] According to these data, over 43,000 women sustain gunshots, stab wounds, broken bones, internal injuries, or loss of consciousness at the hands of current or former intimate partners. In addition, over 57,000 women are raped or sexually assaulted by intimates; over 390,000 sustain minor injuries such as bruises, cuts, or swelling. Up to one third of women injured in domestic assaults seek medical care at emergency departments or community clinics.[3] Of the 1800 murders attributable to intimates in 1996, nearly three out of four had a female victim.[2] Furthermore, about 30% of murdered women were killed by intimates. Although domestic violence disproportionately affects women, men comprise about 15% of assault victims.[2]

In light of the high prevalence and seriousness of injuries, the medical system has been criticized for its inadequate response to adult victims of domestic violence.[4,5] Some researchers have found that the majority of patients experiencing domestic violence are not identified in the medical system and thus do not receive appropriate social, legal, and psychological services.[6,7] Barriers to identification may include time constraints, lack of training, discomfort, and a sense of powerlessness on the part of healthcare providers.[8-10] In addition, patient disclosure of domestic violence may be hindered by their embarrassment, denial, and fear of retaliation by the abusive partner.[11,12]

In an effort to improve the healthcare response, several states have passed mandatory reporting laws that require healthcare providers to report to the police injuries caused by adult domestic violence. Almost every state has laws that require reporting injuries due to deadly weapons, criminal acts, or violence,[13] and these laws potentially apply to injuries that result from domestic violence as well. Five states have mandatory reporting laws that more specifically address reporting suspected cases of domestic violence injuries: California, Colorado, Kentucky, New Hampshire, and Rhode Island.[14-18] Mandatory reporting laws in the Western states are described in Table 1. Most states have separate legislation that governs mandatory reporting for suspected abuse and/or neglect of dependent or incapacitated adults and elders.[19]

The California mandatory reporting law was sponsored by San Francisco Bay Area Assemblywoman Jacqueline Speier in response to a group of prenatal nurses who advocated for a legislative mandate to protect pregnant patients and their unborn fetuses from domestic violence.[20] The proposed legislation (AB 1652) was an amendment to existing laws that required healthcare providers to report to police any injuries caused by deadly weapons or felony assault, including sexual assault. In 1994, the California bill was passed by the legislature and signed into law. This statute requires that healthcare providers report to police all cases in which they

Table 1 *Legislation governing mandatory reporting of injuries in the Western States**

California	Healthcare providers must report to the police if they provide medical care to a patient who they reasonably suspect has a physical injury that was caused by a firearm or other deadly weapon, or by "assaultive or abusive conduct."[14]
Colorado	Physicians must report to the police if they attend a patient with an injury that the physician has reason to believe involved a criminal act, including injuries resulting from domestic violence.[15]
Oregon	Physicians must report to the police if they are treating a patient who they have reasonable cause to suspect has an injury that was intentionally inflicted with a gun, knife, or other deadly weapon.[21]
Montana	Healthcare professionals must report to the police if they treat a victim of a gunshot wound or stabbing.[22]
Arizona	Healthcare providers must report to police if they treat a patient for gunshot, knife, or other "material injury" that may have resulted from an illegal act.[23]
Idaho	Healthcare providers must report to police if treating a patient who they have reason to believe has received any injury inflicted by a firearm or that resulted from a criminal offense.[24]
Nevada	Healthcare providers must report to police if treating a patient with an injury which appears to have been intentionally inflicted by a firearm or knife.[25]
Utah	Healthcare providers must report to police if treating a patient with an injury inflicted by a gun, knife, or other deadly weapon, or by violation of any criminal statute.[26]
New Mexico, Washington	No statutes found governing injury reporting.

*Healthcare providers should review the statutes in their state to guide them through its provisions. The definition of healthcare providers varies from state to state; it typically includes physicians and nurses, but may be broadly defined to include all persons licensed to provide health services.

provide medical care for an adult who has an injury suspected or known to be the result of "assaultive or abusive" conduct,[14] defined to encompass 24 separate criminal acts including "abuse of spouse or cohabitant." Providers are required to notify the police by telephone immediately, or as soon as practically possible, and to submit a written report within 2 days. The report must include the name of the victim, the victim's whereabouts, the extent of the victim's injuries, and the identity of the alleged perpetrator. The statute also contains recommendations for additional documentation in the medical record and victim referral to local domestic violence services. Health practitioners who make reports are protected from civil or criminal liability. Failing to report is a misdemeanor, however, and penalties may include fines up to $1000 or a jail sentence up to 6 months or both.

Since its passage, the California law has created controversy within the healthcare, advocacy, social service, and law enforcement communities. Like much legislation, California's mandatory reporting law has both intended benefits and potential risks. The following discussion and debate is intended to raise both ethical and practical considerations in evaluating the possible outcomes of mandatory reporting of adult domestic violence injuries.

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In favor of mandatory reporting

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It wasn't long ago that when the police responded to a domestic violence call, one officer would take the batterer around the block to "walk it off" while another officer stayed with the victim to "calm her down." Thankfully, that procedure has changed.

It wasn't long ago that if the victim of domestic violence told the police or district attorney that she did not want to "press charges," the matter was quickly dismissed. Nowadays most, if not all, prosecuting attorneys' offices have adopted a "no-drop" policy, which means that every case of domestic violence will be pursued if legally possible.

It took many years of advocacy and perseverance to change the way in which law enforcement officials respond to domestic violence. Healthcare providers should be held to the same standard. California's legislation that requires healthcare providers to report domestic violence injuries has successfully improved the response of the healthcare system to domestic violence, enabling the criminal justice system to enforce the law better.

As institutions respond, professional training increases

Since the mandatory reporting legislation was enacted, we have seen a dramatic increase in the commitment made by healthcare institutions to address domestic violence. A few years ago, only 54% of emergency departments in California reported having policies and protocols for managing victims of domestic violence.[1] Today they often have standardized injury forms, information packets for patients, cameras for documenting injuries, and social service workers poised to intervene. We also have seen greater cooperation among healthcare institutions, law enforcement agencies, social services, and domestic violence advocates.

Mandatory reporting requirements have also increased professional training and continuing education on domestic violence issues. Because healthcare providers are now legally liable for reporting, they are motivated to acquire greater knowledge and skills. This training increases knowledge, comfort, skills for effective inquiry and intervention, and even screening practices.[2,3] The demands, funding, and resources for these domestic violence programs would likely disappear if mandatory reporting by healthcare providers were repealed.

Better identification, treatment, and documentation

Without question, mandatory reporting has improved the identification and treatment of those suffering from domes-

tic violence. Even those patients who present vague stories are now encountering healthcare providers who are familiar with the "red flags" of domestic violence. Trained healthcare providers can demonstrate concern, ask critical questions, and create an environment where patients feel safe. They can communicate to victims that domestic violence is no longer considered simply a "family matter," so they will not be judged for being in such a relationship.

Mandatory reporting potentially improves documentation of domestic violence for use in criminal prosecution, divorce, child custody, and civil cases. Medical records and, less commonly, physician testimony have long been used in both civil and criminal cases as evidence of a history of domestic violence. California's mandatory reporting law strengthens this tradition by requiring healthcare providers to be specific about the cause of injury and the name of the perpetrator. In addition, the statute recommends that providers improve medical recordkeeping by including a body map of the injuries and information about past domestic violence.[4]

Holding the perpetrator responsible

Mandatory reporting sends a clear message to the victim and to society that domestic violence is a crime and will not be tolerated. It is essential that our law enforcement agencies hold the batterer accountable, through incarceration or court-ordered counseling. The strongest deterrent to continued violence is the threat of incarceration,[5] and prosecuting attorneys in California are able to convict batterers without the cooperation or participation of the victim.[6] Failing to report domestic violence injuries is tantamount to aiding and abetting a batterer and deprives the victim of the opportunity for the criminal justice system to work.

AP Photo/Madison & Madison Public Relations

One of a set of posters sponsored by Bell Atlantic Mobile, displayed at the 32 state domestic agencies

Enhancing patient safety

Although opponents to the law suggest that reporting to police may cause retaliation by the batterer,[7,8] we believe that the violence is more likely to escalate in the absence of intervention. The healthcare provider's report to police provides an opportunity for intervention, which may be the only hope of stopping the violence. Domestic violence is a prelude to murder. For many victims, it is only a matter of time. Mandatory reporting by healthcare providers gives victims and their children a chance at survival in an environment free of violence.

Upholding patient autonomy

Under the California law, patients do not retain the right to refuse reporting. They do retain the right to refuse to interact with the police or social service providers, and thus their fundamental autonomy is upheld. Ten years ago, mandatory reporting of sexual assault crimes was harshly criticized for its paternalism. Interestingly, it is now widely accepted that sexual assault is a serious crime warranting law enforcement involvement, no matter what the circumstances of the victim or the relationship with the sex offender. Much like domestic violence, the victims of sexual assault are typically competent adults who have experienced a violent crime, often at the hands of someone known to them.

An opportunity for patient education

Often, through emotional support and honest discussions, patients can be persuaded to cooperate with law enforcement. These discussions provide an opportunity to educate victims about the risks to themselves and their children, their legal options, and opportunities for shelter and support in their community. Although victims may want to avoid family disruption, they need to understand that the violence and abuse are not in their family's best interest. In fact, these discussions can help many victims find the resolve to leave their abusive partners in order to protect their children.[9] Patient education shifts the responsibility for the violence from the victim to the batterer.

Protecting providers from liability

Among healthcare providers, before the legislation was enacted, ambiguity existed about reporting domestic violence. This ambiguity created conflict and fear and left healthcare workers wondering if they had done the right thing. Today, the mandatory reporting law gives healthcare providers protection from liability, as well as clear directions on how to proceed with a patient.

Professional and ethical imperative

There will always be room for individual judgment, but healthcare providers need to bear in mind their obligations to avoid causing harm, to prevent serious injury, and to act for the benefit of the patient. Consider the case of the emergency department practitioner who treated a domestic violence victim. Despite police and social service efforts, the patient was gunned down by her batterer the following morning. As the practitioner so poignantly stated, "I recognized the signs, I was able to get her to tell her story. I know that I did everything, along with the police and the advocate, to try to help her. I can't imagine how I would feel if I had done nothing."[10]

Conclusion

Some healthcare providers may feel that reporting will not stop the violence or protect the victim. They should recognize that this sentiment is an institutional form of learned helplessness. We have the capability to make a positive impact on the victims of violence every day. We need to work together to combat the feeling of institutional helplessness. As professionals, we all have a role to play in protecting victims of domestic violence and holding our colleagues accountable to sharing the commitment to stop domestic violence. For healthcare providers, mandatory reporting is the first step to forming collaborations with other professionals who assist victims of domestic violence. If a healthcare provider were driving home from work and saw a domestic violence assault in progress, one would hope he or she would call the police. Should it be any different in the workplace?

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In opposition to mandatory reporting

- Joanna was treated in an emergency department for facial injuries caused by abuse. A report was made to the police that resulted in her husband's arrest in the hospital waiting room. Joanna returned home, thinking she was safe. Unfortunately her husband had been released and was at home waiting for her. She returned to the emergency department later that day with more severe injuries.
- Donna was injured by her boyfriend. She went to the hospital but was afraid to enter because of the reporting law. She spent the night in her car in the hospital parking lot and did not receive necessary medical treatment.
- Susan attended her prenatal appointment with a fractured hand. She spoke about her boyfriend's violence. When told that a report would be made, Susan became furious about the breach of trust and threatened to walk out of the clinic. To convince her to stay, the physician agreed not to report; instead, she documented the abuse and discussed the patient's options. The patient has continued to see this physician. They are working together on safety planning.[1]

California's law mandating that healthcare providers report domestic violence injuries to law enforcement invokes fundamental professional and ethical questions for healthcare providers and may pose significant health and safety risks for patients.[2]

Places patients at risk for retaliation

Mandatory reporting may place some battered patients at risk of retaliation by the perpetrators. Batterers often escalate the violence if their partners seek outside help or attempt to leave the relationship.[3, 4] Some batterers not only threaten retaliatory violence but also inflict further assaults during criminal justice proceedings. Although healthcare provider reporting may relieve some patients of the onus of reporting, other patients may be blamed by the perpetrator for revealing the source of their injury.

Serves as a deterrent to seeking medical care

Many domestic violence survivors prefer not to involve the police as a remedy for their situation. For example, some battered women might believe that the safest way for them and their children to escape further abuse is to go to a battered woman's shelter rather than to call the police. If these survivors know that healthcare providers will make a report

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despite their objections, they will likely refrain from telling their providers of the violence or from seeking care at all.[5] Some perpetrators may also prohibit their current or former partners' access to health care when it is suspected that reports are being made. Mandatory reporting may particularly jeopardize the health of battered women who are undocumented immigrants, because they might fear that a visit to the doctor could result in their deportation. By limiting access to health care, this law also deprives survivors of the benefits of provider referrals to community agencies, legal services, and the criminal justice system.

Does not improve patient care

Mandatory reporting alone does nothing to ensure that providers will provide appropriate care to battered patients. Untrained and unskilled healthcare providers may be capable of making a police report but unable to provide the necessary support, education, and longitudinal care to patients. Some providers may even rationalize that making a report answers the problem, thus negating their responsibility for ongoing care. Providers who oppose reporting may choose not to inquire about domestic violence at all, thereby depriving patients of potentially beneficial interventions. A more effective and safer means of increasing identification, thereby improving care, would be to enhance provider education and awareness about domestic violence. We believe that any recent improvement in the healthcare response to domestic violence in California is due to major statewide educational initiatives and not to—but rather occurred despite obstacles posed by—mandatory reporting laws.

Creates expectation of services and protection

California's mandatory reporting law does not specify how law enforcement should handle the reports of healthcare providers. In fact, jurisdictions across the state vary widely in their policies and procedures for handling these reports.[6] If there is no effective response to reports of domestic violence, a mandatory reporting law may create expectations of services and protection that cannot be met. This shortcoming could ultimately decrease patient trust in medical providers and the health system, diminish patient safety, and undermine the goals of punishment and deterrence.

Results in inconsistent and biased reporting

Although epidemiologic data on domestic violence injuries are essential, data collected through mandatory reporting may be incomplete and unreliable. Compliance with reporting laws may be low because of lack of awareness of laws, failure of providers to identify cases, opposition to mandatory reporting, and concern that police will not adequately respond.[7] There are ways to collect data, such as anonymous reporting, that do not put patients at risk or jeopardize their autonomy. Mandatory reporting may also result in disproportionate reporting of low-income and minority patients—as has been shown with child abuse reporting[8]—thus perpetuating harmful stereotypes.

Violates the doctrine of nonmaleficence

California's mandatory reporting law effectively removes the ability of healthcare providers to decide what is best for their patients. Consequently, providers may experience conflicts between the mandate to report cases of domestic violence injuries, the patient's desire not to report the violence, and their own judgment of what is in the best interests of the patient. Although reporting domestic violence injuries may, in some cases, lead to punishment of perpetrators and prevent further violence to the patient, in others, it may not be in the best interests of the patient. Some survivors may have already found that calling the police does not stop the violence, and may actually cause it to escalate. If the patient does not want police involvement, it is ethically troubling to override those objections, particularly because healthcare providers have little or no control over the level of protection that their patients subsequently receive.

Undermines patient autonomy

Competent informed adults should be given the freedom to act in accordance with their values and goals.[9] Some survivors of domestic violence do not want their injuries reported because they believe that such a report will be ineffective or even counterproductive. Refusals such as these do not indicate impaired decision-making on the part of the patient. Domestic violence survivors are generally better situated than anyone else to assess their level of personal risk and the type and timing of action that would minimize that risk.

Because of its inherent paternalism, mandatory reporting legislation may be particularly detrimental to patients who are experiencing domestic violence. As part of their healing process, survivors of abuse need to reclaim their own sense of control and to be empowered to make decisions in their best interest. This legislation perpetuates harmful stereotypes of domestic violence survivors as passive and helpless. It interferes with self-determination and may revictimize battered patients by controlling decisions in their lives. The role of healthcare providers should be to render medical services, to counsel and refer to the proper agencies, and to empower and assist patients in choosing among a multitude of available courses of action, including calling the police.

Violates confidentiality and trust

Confidentiality of medical information encourages people to seek medical care and discuss sensitive issues with providers, fosters trust in the doctor-patient relationship, and respects patient privacy.[9] Battered patients often con-

sider trust to be an essential aspect of their relationship with healthcare providers.[10] Breaches of confidentiality undermine trust, deter patients from confiding in their providers, and may harm patients in more tangible ways as well.

Exceptions to confidentiality are justified in order to prevent serious harm to third parties, such as those at risk for infectious diseases, and to identify and protect persons who are incapable of seeking assistance on their own.[9] Such exceptions are warranted when the benefits of the intervention are substantial and the harms resulting from the breach are minimized and acceptable. In the case of domestic violence, however, the harm to third parties is unclear, battered patients have intact decision-making capacity, and imposed interventions are of unproven benefit.

Conclusion

Domestic violence is a nationwide epidemic with significant health consequences, including emotional trauma, physical injury, and even death. As such, it requires a collaborative approach involving healthcare providers, community domestic violence agencies, law enforcement officials, and, most importantly, the patient. Mandatory reporting laws, though well-intentioned, are of unclear benefit in enhancing the safety and well-being of patients who have experienced domestic violence. Mandating a coercive intervention that fails to offer adequate protection may further jeopardize the patients we are trying to serve. Mandatory reporting may threaten the safety of battered patients, will likely discourage them from seeking care and accessing services, does little to improve their health, may result in biased case identification, and violates patient autonomy and confidentiality. The role of the healthcare provider is not to serve as an arm of the criminal justice system, but rather to deliver optimal health care. In the case of domestic violence, this includes informing patients of their options (police involvement being but one of them) and helping them access those the patients believe will enhance their safety and well-being.

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The way forward

Unfortunately, the discussion about the potential risks and benefits of California's mandatory reporting law is based on well-intentioned conjecture and anecdotes rather than a formal evaluation of the law. While the contributors to these articles may disagree on the implications of California's mandatory reporting legislation, there is consensus regarding the continued role of healthcare institutions, medical providers, researchers, and policy makers in improving the medical response to abused patients. The following themes for improvement emerge from the debate on mandatory reporting.

Conduct research to document both beneficial and harmful outcomes of reporting

At present, little is known about the actual impact of the California law on local law enforcement and district attorneys' offices, healthcare institutions, community-based social service and advocacy organizations, and victims of domestic violence. Thus far preliminary research has failed to demonstrate any significant increase in the number of domestic violence injury reports from healthcare institutions.[1]

Investigating the impact of mandatory reporting in California is complicated by recently enacted legislation. As a complement to current Joint Commission on the Accreditation of Healthcare Organizations requirements,[2] the 1995 amendments require hospitals and medical directors to establish written policies and protocols for screening patients for spousal and partner abuse.[3] The impact of these legislative changes may be reflected by the increase in the number of emergency department protocols for adult victims of domestic violence, from 43% in 1993 to 79% in 1997.[4]

The attitudes of California physicians and patients toward mandatory reporting appear conflicted. Abused women have reported that although police intervention may hurt them, by inciting anger and retaliation, it also may help them, by providing protection.[5] Similarly, while most California physicians agree that reporting potentially interferes with the doctor-patient relationship, most physicians also agree that the law may improve the healthcare and law enforcement response to domestic violence.[6]

Research on the experiences and perspective of battered patients, particularly those who have been report-

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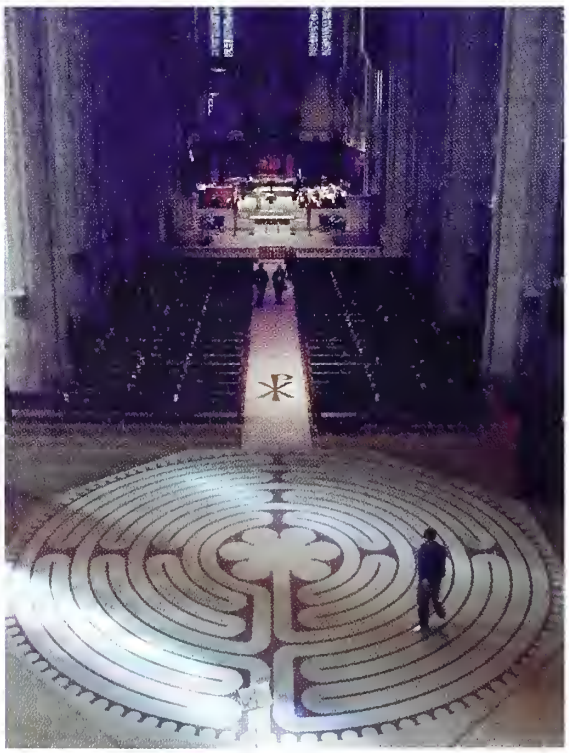
ed by a healthcare provider, is essential in assessing the impact of the legislation. In 1998, a National Academy of Sciences committee for the Institute of Medicine recommended that "states refrain from enacting mandatory reporting laws for domestic violence until such systems have been tested and evaluated by research."[7]

Provide professional training and institutional support

Education, training, and the use of clinical guidelines for identifying and managing victims of domestic violence[8] will continue to be a major force in improving providers' effectiveness and sensitivity. Already, the California legislature has amended physician and nurse licensing requirements to include training in the detection and treatment of spousal and partner abuse.[9] Healthcare systems have an important role in instituting changes that facilitate and support interventions for domestic violence victims, including developing protocols, providing staff training, and evaluating progress through quality assurance procedures.[10]

Support and expand victim services

Another point of consensus is that legislators should make a commitment to improve the services provided by law enforcement, court systems, social services agencies, and community-based organizations. Shelters and community-based services need to be better funded, expanded to meet the needs of rural areas and culturally diverse communities, and coordinated with health and legal systems to create a comprehensive network of victim support.



AP Photo/Susan Ragan

A solitary man walks across the prayer labyrinth at Grace Cathedral in San Francisco. Bay area churches held worship on 'The Gentle Life' last January to combat the domestic violence that escalates on Super Bowl Sunday.

Consider policy alternatives

Although policy makers have an important role in improving the healthcare response to domestic violence, they need to consider the implications of different mandatory reporting provisions. The American Medical Association (AMA) proposed that mandatory reporting statutes include provisions that protect patient identity, allow competent adults to opt out of the reporting system, require reports to public health agencies, and include evaluation components.[11] In addition, the AMA suggested incorporating a sunset mechanism in which the legislation would be in effect only for a limited number of years. The legislative process must involve collaboration among professionals (medical, social service, legal) and domestic violence advocates and victims, and it must be informed by well-designed research on the impact of mandatory reporting.

Conclusion

In California, the law's recent implementation, its uniqueness, and its potential to serve as model legislation in other states highlight the importance of setting a research agenda to assess the impact of the mandatory reporting legislation. Ideally, policy should be based on sound scientific knowledge, but this has not been the case for mandatory reporting. Considering the seriousness of the issue and the investment so far, a more scientific approach to policy implementation must become a priority.

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Mandatory reporting: the view from the community

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The law that mandates physicians to report domestic violence to law enforcement officials involves practitioners in community responses. When practitioners call the police, they open a door into territory that is often unfamiliar to them and their patients: the realm of criminal justice and social welfare. Physicians can improve their impact on domestic violence by better understanding the processes and agencies involved in community responses.

Summary points

- The common goal in a community's response to domestic violence is the safety of battered women and their children.
- A phone call to a law enforcement agency is not enough to insure a woman's safety.
- Most domestic violence crimes are charged as misdemeanors. Batterers are often released after only 12 to 48 hours in jail.
- Shelter service programs support battered women and children as they develop safer lives.
- A domestic violence coordinating council provides the means to be an effective partner in a community response network.

What happens in the hospital

Ideally hospitals and medical associations have protocols with local law enforcement agencies and the battered women's support system that include having trained staff available to talk with a patient about the evidence of abuse, the need to contact the police, and what to do next to be safe. Before the police are called, staff would tell her about the services of the battered women's support system and suggest that she call them. If possible, a battered women's advocate would meet with her before the police arrive.

According to the mandatory reporting law, physicians are only required to complete and file a written report documenting injuries. If those are the only steps they take, however, physicians are likely to see battered women again—especially if abusers are not effectively held accountable. A recent mortality study in Florida reports that 88% of victims of domestic violence fatalities had a documented history of physical abuse.[5] Physicians depend on the criminal justice system to keep their patients free of injury by keeping the batterer at bay. Physicians' medical records of recurring injuries are testimony to an imperfect, or failing, system.

How does the system work and how can physicians help?

The common goal for everyone involved in the community response is the safety of the battered woman and her children. Each participating professional attempts to insure her safety in different ways.

Officers gather evidence of a crime, assign a charge based on the criminal codes, arrest the perpetrator of the crime, transport him or her to jail, and submit reports to criminal court. They may also be called upon to uphold a stay-away order filed in civil court by the victim or to testify in court. All their protective actions must be based on clear evidence of a crime. Savvy abusers know how to harass, assault, and get away before police can respond, leaving no hard evidence. In one study, 60% of women reported acts of abuse after the entry of a protective order, and 30% reported acts of severe violence.[5]

The medical evidence, especially a body map or X rays, is sufficient for an arrest and may be the only evidence available. To avoid having to testify in court, practitioners are advised to leave the task of photographing injuries to the police. Also, time is needed for bruising to appear. The police response time to a call, their care in not frightening other patients with their presence, and their approach to patients all improve dramatically when physicians provide reports in formats that officers can use easily. Medical staff may benefit from contacting their chief(s) of police and sheriff, who can work with their officers so that good practices can be disseminated and protocols can be modified when they go awry.

There are about 1500 domestic violence shelters with advocacy and support programs in the United States. Funding, politics, and philosophies affect the capabilities of these battered women's programs. In California, most programs offer 24-hour phone access to a crisis advocate who helps victims assess their options: transportation to safety, shelter in safe places for up to 45 days, securing protective orders, attending criminal and civil court, peer counseling, finding more permanent housing, and making connections to social services.

Support programs are usually nonprofit organizations staffed by paraprofessionals, mostly women. Their role is to support women and their children as they develop safer lives. When a woman tries to leave a batterer, it is key to keep the shelter location secret. Any local shelter or support program can be found by calling the National Domestic Violence Hotline at 1-800-799-7733.

Physicians may benefit from meeting support providers to find out what services they offer and to develop effective protocols for working together. Questions to ask: Do they have staff who can come to a hospital in the night? How much room do they have in their shelter? Do they have language interpreters? Do they have ethnically diverse and lesbian staff workers? Do they serve battered men? What are their policies about helping women with substance abuse or mental health problems?

Abuser accountability is often the least developed component of the community response system. The district attorneys and judges in the legal system have broad discretionary powers. Removed from the immediacies of seeing the contusions and broken lives of battered women and their children, they rely on the reports of third parties or the testimony of the frightened victims. Many abusers deny their offences when communicating with officials.

Laws are changing rapidly. Many judges, burdened with overcrowded schedules, are simply uninformed about the dynamics of domestic violence and changes in current laws. Like the district attorneys, they are under pressure to avoid costly trials. Unless there is well-documented evidence of grave bodily harm, or unless guns and drugs are involved, most domestic violence cases are reduced from felonies to misdemeanors and the batterer is set free within days, even hours, of arrest. He may be required to attend a weekly batterers' program, but these programs have not proved effective in preventing future violence.

Women are often in graver danger when the police become involved.[6] Physicians should always tell women when they plan to report injuries to the police, and women need to develop safety plans, with or without the help of shelter advocates. Many communities are creating domestic violence task forces or coordinating councils that meet to educate, crosstrain, and develop protocols and community education strategies. It takes time to learn the language of different professions and to understand each other's perspectives and constraints. Most task forces or councils try to include among their membership shelter advocates, law enforcement officials, representatives from the district attorney's office, judges, and personnel from victim witness, probation, and batterer treatment programs. In recent years, more public health and maternal child health professionals have joined these efforts.

Domestic violence councils can be found by calling the shelter program or the district attorney's office (listed in the phone book under county government). Because physicians are seen as colleagues of judges and district attorneys, their reports of the frequency and severity of injuries to victims of domestic violence, including children, may be more influential than those from advocates or police.

Useful Web pages

American Medical Association: ama-assn.org

Domestic Violence Project of Santa Clara County: www.growing.com/nonviolent/index.htm

Family Violence Prevention Fund: www.igc.org/fund/

Minnesota Center Against Violence and Abuse: www.mincava.umn.edu

National Coalition Against Domestic Violence: www.ncadv.org/links

What about the emotional side?

In the dynamics of domestic violence, there are complex emotional responses that all the best planned and most coordinated responses may fail to touch. For example, there is the compulsion in a person to control his partner, which means that he continually assaults her, even after being arrested, sent to treatment programs, or even sent to jail. When a woman decides to go back to live with a person who belittles and brutalizes her, minimizing the pain she has experienced and counting on love or hope to alter his behavior, there are emotions at work that keep her from responding to outsiders' best offers to help. These dynamics trigger reactions in everyone involved, and they can frustrate the efforts of everyone working together to minimize domestic violence. What they may show, however, is preventing patterns of abuse may require addressing the social and emotional roots of that abuse.

Conclusion

In the area of domestic violence, society has come a long way in a relatively short time. The first shelters for battered women opened in 1964. In 1992 the American Medical Association released guidelines suggesting that doctors screen women for signs of domestic violence. Maryland passed the first state law that made wife-beating a crime in 1882. Whether or not it is wise to mandate medical practitioners to report evidence of domestic violence, the Mandatory Reporting Law passed in 1993 has done a service to the community by making the medical profession aware of the magnitude of the problem and the need to join others in alleviating it.

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Pathography: patient narratives of illness

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Introduction

In ever greater numbers, people are writing autobiographical accounts of their experience of illness and treatment, narratives that are often called pathographies or autopathographies.[1-4] Increasingly patients are turning to these narratives for anecdotal information about particular illnesses and their treatments, conventional and alternative. Hence the remarkable popularity of such books, many of them bestsellers.

Pathographies not only articulate the hopes, fears, and anxieties so common to sickness, but they also serve as guidebooks to the medical experience itself, shaping a reader's expectations about the course of an illness and its treatment. Pathographies are a veritable gold mine of patient attitudes and assumptions regarding all aspects of illness. These narratives can be especially useful to physicians at a time when they are given less and less time to get to know their patients but are still expected to be aware of their patients' wishes, needs, and fears.

There are some 60 pathographies now in print about breast cancer alone. They describe orthodox treatments from lumpectomy to bone marrow transplant and alternative treatments from orthomolecular therapy to psychic healing. Prostate cancer pathographies are on the increase. In many, authors detail the way they aggressively seek out "the best" urologist and "the best" cancer center. Pathographies about HIV and AIDS are plentiful: an Online Computer Library Center search reveals 31 were in print in 1992, and the number had increased to 74 by 1997.

By writing pathographies, patients not only restore the experiential dimension to illness and treatment but also place the ill person at the very center of that experience.

Personal narratives about psychiatric disorders, especially bipolar disease, are also flourishing. Pathographies about disability become more varied as the mortal illnesses of yesterday are transformed into chronic illnesses today. Reynolds Price emphasizes the problems of living with paralysis rather than the spinal cord tumor that is its cause; similarly, Barbara Barrie focuses not so much on her colorectal cancer as on how she leads a happy and productive life with a colostomy.[5,6] Neurological disorders of all kinds are subjects for pathography, from common diseases like epilepsy and Parkinson's to rare illnesses such as facial neurofibromatosis and Tourette's syndrome. There are now personal narratives by individuals who are so severely disabled—some hooked up to respirators and feeding tubes and some with conditions such as endstage ALS, locked-in syndrome, and autism—that the act of writing itself is an extraordinary achievement. Autopathographies about dying (often including near-death experiences) and biopathographies about the death of a loved one are becoming more numerous. Many reflect national trends, describing a hospice death or some form of assisted dying.

Physicians will want to read some of these books to find out just what it is that makes them so compelling to patients. The annotated appendix in this author's Reconstructing Illness, organized around disease categories, might be useful in directing readers to particular pathographies.[2] Individuals with a particular interest in breast cancer, HIV/AIDS, or disability will want to look at Thomas Couser's discussion of such pathographies in Recovering Bodies.[4]

My aim in this discussion is to provide an overview of pathography that addresses the following questions: (1) What kind of people write book-length narratives about their experience of illness? (2) Why do they write them? (3) What can physicians learn from these narratives?

The tradition of pathography

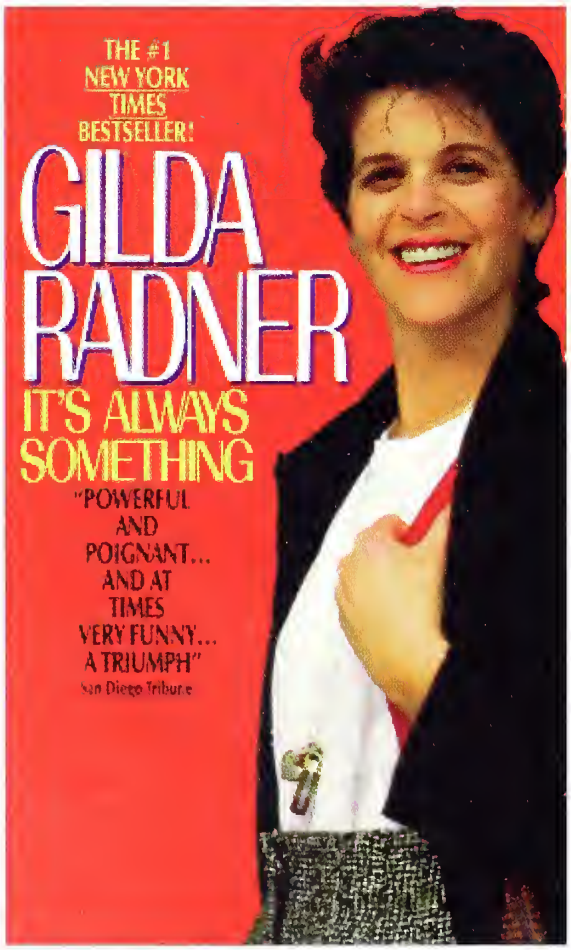
Well-known authors and public figures do write pathographies.[5,7-11] For the most part, though, authors of pathographies are a heterogeneous group: movie stars, hairdressers, housewives, ministers, journalists, athletes, truck drivers, and college teachers. They do not include the very poor; indeed, most are middle class. Racial minorities are better represented in recently published pathographies, though such authors tend to belong to the middle class. Religion—Christianity in particular—provides the perspective on illness in a substantial number of pathographies.

A striking aspect of the genre is that it appears to be a recent phenomenon. With a few exceptions, such as John Donne's 17th-century Devotions or sanatorium narratives from the 1920s and 1930s, pathography seems to

belong exclusively to the second half of the 20th century.[2,12,13] There are innumerable diaries and journals from earlier eras that include descriptions of illness, but few of these take the author's experience of illness as their only subject.

Why should people be writing illness narratives today in such numbers? One explanation is that in earlier times, sickness was considered an integral and inseparable part of living and dying. Thus sickness took its place in an individual's memoir alongside other experiences in life. Another explanation points to the sense of depersonalization that many feel about medical treatment today. By writing pathographies, patients not only restore the experiential dimension to illness and treatment but also place the ill person at the very center of that experience.

In a sense, the autobiography about illness can be seen as complementing a patient's medical record.[2,14] Both kinds of writing concern the sickness and treatment of a specific individual, but the contrasting points of view—the patient's versus the medical staff's—make an enormous difference. Case reports are generally about a biomedical condition and its treatment; pathographies, on the other hand, concern illness and treatment as it is understood by the ill person. They differ in subject and in composition. The medical report is usually made up of impersonal statements by medical caregivers about symptoms, test results, and response to treatment. A pathography is an extended single-author narrative, situating illness and treatment within the author's life and linking them with the meaning of that life. Pathographies provide the story of illness from the perspective of the individual patient.



Autobiography of Gilda Radner.

What value is it for physicians to read a single book narrating a single individual's illness experience? Are these books generalizable in any way? The answer is yes. One can categorize a pathography by the disease that is its subject, by dominant myths, attitudes, and assumptions, and by the author's intent in writing the book.

Four types of pathography

Four different groups of pathographies emerge when one analyzes them according to authorial intent.[2] The first might be called "didactic pathographies." These narratives are motivated by the explicit wish to help others. Often they blend practical information with a personal account of the experience of illness and treatment. Descriptions of breast cancer experience, for example, have enabled women to become aware of therapeutic alternatives—both within and outside conventional medical practice. Other pathographies concern culturally problematic issues, such as assisted death, HIV discrimination, or the use of alternative medicine, and are based on the assumption that the author's experience can serve as a mirror or a model (whether positive or negative) for prospective readers.

A second category consists of "angry pathographies." Authors of these are motivated by a strong need, based on personal experience, to point out deficiencies in various aspects of patient care. Nearly always, these are deficiencies of empathy. As one pathographer observes about her lengthy hospitalization, "I was no longer afraid of the disease, but of the system."[15] Pathographies of this kind are important in alerting all of us to important problems in medical practice. They vividly depict how an ill person today can be at the same time the beneficiary and the victim of a healthcare system whose very excellence—its superb technological and pharmacological achievements—is at the same time potentially dehumanizing.

A third type of narrative, the "alternatives pathography," is also critical of our medical system, but without angry denunciations or doctor-bashing. Like their angry counterparts, these pathographies stem from dissatisfaction with medicine. They differ in that the author is concerned not so much with criticizing traditional medicine as with finding alternative treatment modalities. One can

find pathographies about every conceivable kind of alternative. A surprising number of authors describe how they combined conventional treatment with one or several alternative therapies, most without telling their doctors. This group of pathographies can be invaluable in alerting physicians to the appeal of alternative medicine and to the specific treatments that attract patients with particular illnesses.

A fourth and very recent group, which might be called "ecopathography," links a personal experience of illness with larger environmental, political, or cultural problems. In these books, illness (usually AIDS, certain cancers, or chronic fatigue syndrome) is perceived as cultural disease, "the product of a toxic environment," as one author observes.[16] The motive of the authors of ecopathographies is prophetic: they are warning the rest of us that their illnesses are the signs and symptoms of much larger problems confronting our culture as a whole. As Kat Duff writes in her pathography, "Illness is the shadow of Western civilization, the antithesis of the rampant extraversion and productivity we so value."[17]

The uses of pathography

The common denominator of all pathographies, whatever the ostensible motives of their authors, is that the act of writing in some way seems to facilitate recovery: the healing of the whole person. For most of us, really serious illness is a painful, disorienting, and isolating experience. It is a trauma, an insult not only to the body but also to the self. As Robert J. Lifton has shown, coming to terms with a traumatic experience often involves the attempt to project it outwards by talking or writing about it.[18,19] Writing about an illness experience is a kind of psychic rebuilding that involves finding patterns, imposing order, and, for many, discovering meaning. Pathography, then, is not only a description of how awful it is to be seriously ill, but also a testimony to the capacity to transform that experience in ways that heal.

For physicians, pathographies can provide a unique "window" into the experience of their patients, often revealing aspects of patient experience that remain unarticulated in the medical encounter. These books can be medically useful for a number of reasons:

- They embody the patient's point of view on a variety of aspects of a medical experience.
- They offer a longitudinal view of illness as it is experienced before and after the patient encounters the physician.
- They describe common issues in medical encounters that are often problematic, demonstrating both helpful and harmful ways in which a physician can deliver bad news; providing concrete examples of physicians who express (or fail to express) empathy; illustrating the patient's dilemma when confronted with conflicting advice from different medical experts.
- They provide information about alternative medical treatments from the perspectives of the patients who use such treatments.
- They reveal cultural attitudes and assumptions about illness, treatment, and recovery (the idea that illness is a battle or a journey, for example), showing how these can help (or fail to help) patients to better deal with their medical situations.

In these ways, pathographies can be helpful not only for the people who write them and the patients who read them, but also for physicians.

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In the Public Eye

Media Watch

Patients for sale: the seamy side of clinical trials

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For physicians who test new drugs and procedures in clinical trials, this hasn't been a good year. One of the federal government's oversight agencies, the Office for the Protection of Research Risks, has used its powers to shut down clinical research at the West Los Angeles V.A.M.C. and at Duke Medical Center in North Carolina (see Media Watch, July 1999 WJM). Meanwhile, some of the nation's leading newspapers have been suggesting that clinical trials harm more patients than they help.

Reporters at the Boston Globe and the New York Times spent months unravelling the underside of clinical trials. Both papers described a dirty business in which physicians knowingly exposed patients to serious risks in order to earn millions of dollars testing new drugs. Using Freedom of Information requests, the two papers obtained court transcripts, notes of hospital injuries, results of clinical trials submitted to the Food and Drug Administration, and records of investigations conducted by the agency.

Their findings made front-page news. The Boston Globe's four-part series ran last November; the New York Times' pair of articles came out in May. For some readers, the papers' efforts may have permanently stained the image of clinical research in this country.

The Boston Globe offered readers what the paper termed "a peek into the financial side of corporate funded research of new drugs." One of the articles in the Globe series described a Minnesota psychiatrist who was a past president of the state psychiatric society and had previously chaired the society's ethics committee. In the course of researching new antipsychotic medications, the psychiatrist, by his own admission, entered "disturbed and vulnerable" psychiatric patients into drug trials, though he knew they did not meet the eligibility criteria. The patients did poorly and at least one woman died. The medical board in Minnesota described the doctor as "reckless" and eventually suspended his license to practice.

After a patient with schizophrenia committed suicide while taking part in a study of an antipsychotic drug, the doctors allegedly bribed staff to keep the death under wraps.

Two other psychiatrists described by the Globe were prominent faculty members at the Medical College of Georgia in Augusta. One chaired the school's psychiatry depart-

ment and the other was a pharmacologist. According to the Globe, the two earned over $10 million during 7 years of conducting clinical trials for numerous drug companies. When the FDA investigated, the agency heard that the two doctors hardly ever saw the patients they enrolled in trials. After a patient with schizophrenia committed suicide while taking part in a study of an antipsychotic drug, the doctors allegedly bribed staff to keep the death under wraps. Their bribery, along with other crimes such as stealing money that was intended for the medical school, enabled the FDA to bring an indictment. Both doctors were found guilty of several charges and sentenced to prison time and fines.

The New York Times ran the first installation of its May series in the Sunday Times, on the front page, above the fold, highlighting the significance of the series. A photograph of a drug company contract stated that physicians who participated in a clinical trial of drugs for migraine headaches would "receive $3,600 for each valid, completed patient." The series was entitled "Research for Hire" and described clinical research as "a multibillion dollar industry." "In this new industry," the Times noted, "patients have become commodities, bought and traded by testing companies and doctors."

The second article in the Times series described a family physician in Whittier, California, who developed a side business as a clinical trialist. In 1997 that business, called the Southern California Research Institute, was raided by the FDA and the doctor was found guilty of fraud. Among other things, the doctor encouraged his research staff to carry out fake lab tests and to falsify lab records. In a table titled "Finding the Loopholes," the Times described several different loopholes as "undetectable" with current oversight procedures.

The Times also claimed that even though informed consent forms for any clinical trial must be approved by ethics boards, and doctors running clinical trials are obliged to present the forms to patients, adequate consent is "not obtained about half the time."

These articles, and the FDA investigations and indictments that they describe, have not gone unnoticed. Already, the president's National Bioethics Advisory Commission has issued a lengthy series of recommendations aimed at ensuring that research with psychiatric patients is conducted in an ethical manner. In the next few months, it is likely that other federal and state agencies will also announce new recommendations and regulations for clinical research.

To media watchers, the Boston Globe and New York Times series represent some of the best reporting on medicine to appear anywhere in the past year. The Globe series was a finalist for a Pulitzer prize in 1998, and few will be surprised if the Times series is nominated for a Pulitzer in 1999.

To view the report of the NBAC: http://bioethics.gov/capacity/TOC.htm

The New York Times articles: http://www.nytimes.com/library/politics/051799drug-trials-industry.html

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News and Features

United States considers ban on British blood

Scott Gottlieb, New York

A federal advisory panel to the US Food and Drug Administration has recommended barring people who visited Britain frequently or for long stays between 1980 and 1996 from donating blood in the United States because of the possible risk of transmitting the human form of bovine spongiform encephalopathy, known as new-variant Creutzfeldt-Jacob disease.

The administration is not bound by the advisory panel's recommendations but generally follows them. New-variant Creutzfeldt-Jacob disease has never been transmitted through blood except during experiments in which it was injected into the brains of mice. But panel members, drawn mostly from the clinical medicine and medical research communities, say that they are concerned that scientists have not fully ascertained how the disease is spread. "The day you find out that there is human transmission, you're too late to protect the blood supply," said Linda Detwiler, senior staff veterinarian for the US Department of Agriculture and a member of the advisory panel.

The American Red Cross is worried that between 35,700 and 2 million units of blood would be lost if the advisory panel's recommendation took effect. Almost 23% of all blood donors have traveled to Britain during the time in question. "These are precautionary measures based on theoretical risks," said Richard Davey, a spokesman for the American Red Cross, which supplies about 50% of blood in the United States. "It's very unsafe not to have enough blood."

AP Photo/David Zalubowski

Blood from the United States is preferred to that from the United Kingdom.

The advisory panel's members were split on the decision, with 12 members voting in favor of the recommendation and 9 voting against it. The panel members were also divided over the question of how much travel time to Britain should disqualify people from donating blood. Some panel members recommended as few as 4 months, whereas others said a year or more.

The Blood Safety Committee of the Department of Health and Human Services is expected to meet soon to consider the issues raised by the advisory panel. This committee has a broader mandate to consider the economic and political ramifications of any decision, and as a result their recommendations are likely to carry more influence with the Food and Drug Administration. If the committee recommends that certain blood products be excluded, the ban could come into effect within a few months.

Surgeons develop composite bone transplants

Deborah Josefson, San Francisco

Composite bone transplants using cadaveric and host bone may become a standard method of repairing bony defects. A 6-year-old boy, Adam Johnson, underwent this pioneering procedure 9 months ago and has shown good results.

Adam lost most of his humerus to cancer and faced the choice of further amputation and a prosthesis or the experimental procedure. Orthopedists at Joe DiMaggio's Children's Hospital and at Shands Hospital in Gainesville, Florida, performed the surgery, in which they fused the humerus from a cadaver to a portion of Adam's fibula and transplanted it to the area of his humerus.

Although cadaveric bone transplants are not new, fusing them to a live bone is. The fusion allows continued bony growth because the host's vascular supply and cartilaginous cap are preserved, a feature especially important for children. If a cadaveric bone alone or a ceramic composite were transplanted, the patient's limb would not achieve adult dimensions.

Commenting on the case, Michael Jofe, a member of the bone transplant team, said, "A recent test has shown that the growth cartilage and blood supply to the transplanted fibula remain intact. There has already been evidence that the bone is growing."

In the United States, about 250,000 people a year undergo orthopedic allotransplants, but only a small number of these are cadaveric. The cadaveric bone is typically tested for infectious diseases and sterilized by gamma irradiation. It may be further prepared by demineralization and by drilling it with laser holes, thought to help incorporate the bone into the host. Unlike patients receiving organ transplants, those receiving cadaveric bone transplants do not require immunosuppressive drugs.

Children exposed to magnetic fields may have more leukemia

David Spurgeon, Quebec

A Canadian study has shown higher rates of leukemia among children who were exposed at an early age to electromagnetic fields in their homes compared with those less exposed. It does not show that these fields cause cancer, however, and a separate US study concludes independently that the evidence for a causal relation is weak.

The Canadian study, carried out by researchers at the University of Toronto and the Hospital for Sick Children, Toronto, with partial funding from the Ontario Hydro Services Company and the Canadian Electrical Association, was reported in two separate papers in the International Journal of Cancer (1999;82:161-170) and the journal Cancer Causes and Control (1999; 10:233-243). The US study was a review and analysis of 6 years of existing data in a report to Congress by the National Institute of Environmental Health Sciences.

Researchers compared 201 children living in the greater Toronto area, diagnosed between 1985 and 1993 with leukemia at up to 14 years of age, with 406 controls. By measuring exposures to electric and magnetic fields inside and outside their homes, researchers found that those with higher exposures were 2 to 4 times more likely to develop leukemia than those less exposed. Risks were higher for children diagnosed at less than 6 years of age and for those with lymphoblastic leukemia.

The lead author, Lois Green, epidemiologist in the university's public health sciences department and at Ontario Power Generation, says that the association between magnetic fields and risk of leukemia became stronger as methods of measuring exposure were refined, particularly in younger children. "But this study does not establish that magnetic fields cause cancer," she said. "To date, laboratory research has not shown a plausible biological mechanism supporting a cause-and-effect relationship."

The US report says that "the National Institute of Environmental Health Sciences believes that the probability that electromagnetic field exposure is truly a health hazard is currently small." The study also found inadequate evidence of any link to other diseases, such as Alzheimer's, depression, and birth defects. This study, too, cited an absence of laboratory evidence for a cause-and-effect relation.

In the US report, however, researchers said that the epidemiological associations cannot be completely discounted. For that reason—and because virtually everyone in the United States is routinely exposed to electric and magnetic fields—"efforts to encourage reductions in exposure should continue."

Pregnancy does not increase mortality in breast cancer

Scott Gottlieb, New York

Women who become pregnant after a diagnosis of premenopausal stage I or stage II invasive breast cancer show no increase in mortality compared with those with no subsequent pregnancy, according to a new study.

The study—one of the first to investigate systematically the effect of pregnancy on patients' survival after a diagnosis of breast carcinoma—followed 618 women in whom stage I or stage II invasive breast carcinoma was diagnosed before the age of 40 years. The diagnoses were all made between the years 1983 and 1992. The researchers compared the 53 women who became pregnant after the diagnosis with 265 matched controls with the disease who did not become pregnant. Results showed no significant difference in mortality (Cancer 1999;85:2424-2432, 2301-2305).

Five of the women who became pregnant eventually died of the condition during the follow-up period, compared with 34 of the women without a pregnancy. The age-adjusted relative risk of death associated with any subsequent pregnancy was 0.8 (95% confidence interval 0.3-2.3). The investigators were unable to control for the stage of disease at the time the pregnancy occurred, however.

"The results of our study support the growing consensus that subsequent pregnancy does not have an adverse effect on survival after breast carcinoma, particularly among women with local disease," said Dr. Priscilla Velentgas of the University of Washington, Seattle, who carried out the research in collaboration with a team from Seattle's Fred Hutchinson Cancer Research Center. The researchers noted, however, that women who became pregnant after a diagnosis of breast cancer had a higher rate of miscarriage. Of those women who became pregnant, about 24% of the women with a diagnosis of breast cancer had pregnancies that ended in miscarriage, compared with 18% of controls of similar age who had never had breast cancer.

In an accompanying editorial, Dr. Hervey Averette from the University of Miami, Florida, commented, "This study addresses an important issue in the management of premenopausal breast carcinoma survivors. This subgroup of patients frequently has questions regarding future childbearing and the risk of recurrence and overall survival due to pregnancy. The study concluded that pregnancy after breast carcinoma does not appear to have an adverse effect on survival."

AP Photo/Remy de la Mauvinière

Pregnancy does not adversely affect survival after breast cancer.

West of the Rockies

Speaker's Corner

Accomplice

They lived far out in the country, took their water from a spring, and heated with wood that he cut himself. He was proud of that. He did a variety of odd jobs all over the county. A jack-of-all-trades, he was a fixture on the North Carolina mountain roads in his old beat-up Ford truck, its bed containing a mound of tools and trash.

She stayed at home, alone. Even if they had had a television, there were no signals that reached into the hollow in which they lived. I imagined her only companion was the local radio station that played sad country and western tunes.

They always came to the office together for their routine visits, a study in contrasts. He had hypertension but was in good shape otherwise, ruddy and vigorously upbeat. A stocky man with short gray hair and gray stubble on his cheeks, he always wore clean but threadbare bib overalls. He was the kind of man you could hear in the waiting room as soon as he arrived, talking to anyone who would listen or, more often, to no one in particular. He did the talking for both of them, mostly about himself, and was so full of opinions that you couldn't shut him up if you tried. He wasn't refined, but he wasn't dumb either. I didn't like him.

I did like her. She always wore the same long print dress with a sweater, white socks, and boots, regardless of the temperature. She was blue from severe chronic obstructive lung disease and bloated from the steroids she had taken for years. Cigarettes were also a companion, I supposed. She was blue in another sense: in her past, there were hospitalizations for psychiatric care. Tricyclic antidepressants now kept her outside those hospital walls.

She responded only to direct questions, never venturing anything spontaneously. She spoke predominantly in soft monosyllables and rarely complained. When she did complain, he would usually dismiss the complaint and redirect the conversation. I thought he was worried about what her complaints might cost him. He was more cost-conscious than any HMO.

One spring morning, rejoicing in the clear mountain air and blooming jonquils, I arrived at the hospital to make rounds but was pulled into the four-bed emergency room. She had just arrived, comatose, and bluer than usual.

He was at her bedside when I walked in. He smiled and shook my hand. "She took a bunch of aspirin," he said matter-of-factly.

I sent him from the room so that I could do my work. After 2 hours she died, drowning in her own fluid, never regaining consciousness, never saying another word, as blue and quiet in death as she had been in life.

Death is shocking to me. I always feel guilty about it. I went to find him. He was having a cup of coffee in our otherwise deserted cafeteria. I sat down across from him in one of those hard stackable plastic chairs and stared across the square Formica-covered table. We listened to Muzak playing in the background and inhaled stale coffee and grease odors. We sat quietly for some minutes. I was unable to speak for fear that tears would come.

"She's gone, isn't she?" he finally asked.

I nodded and started to speak, but he cut me off. "Well, she'd been sick for a long time," he said.

He arose, walked out to his truck, and drove away. I figured he wanted to grieve in private. I was amazed by the unexpected quiet dignity in his act and relieved that he had made my job easier. Somehow, his quiet exit seemed to absolve me. Perhaps I had misjudged him.

About a month later, I saw him in the office for his routine visit. I was uneasy and unsure about how to deal with him in her absence.

"How are you, Doc?" he said, almost yelling, as I walked in the room.

"I…I'm fine," I stammered. "I never got to tell you how sorry I am for your loss. I hope you're doing okay. I know how terrible that day must have been for you."

"You know, Doc, when I got home the night before she died, she was acting a little strange. But that wasn't uncommon for her." He chuckled. "Later, just after we went to bed, she vomited. I figured it was something she ate. That morning when I woke up, she was still in bed. I couldn't wake her up. Then I found the empty aspirin bottle. She'd done this kind of thing before, you know. About a week before, in fact, she tried to shoot her-

self with my shotgun. Blew a hole in the ceiling when she missed. She seemed okay afterwards, though."

He shook his head and shrugged. "Anyway, I'm doing great. I got married again. Happiest I've been in years."

I had been standing as he talked to me, but now I had to sit down so that I would not faint. Somehow, I made it through that visit. He even introduced me to his new wife.

She seemed quiet.

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Reflections of a "medical specimen"

see also p.92

Mark Gash, Hollywood, CA

Mark Gash is a 43-year-old oil painter, actor, and Internet website designer who lives with his dog in an apartment in Hollywood, California. He also lives with osteogenesis imperfecta #3, a severely crippling skeletal disease. Mark's appearance has exposed him to decades of negative stereotypical misperceptions—by society and doctors—of people with developmental disabilities. He describes his experiences in this article, which was edited from a videotaped interview conducted by David Doostan, MD, and Michael Wilkes, MD.

Some of the most difficult parts of growing up disabled, especially when I was a kid, were people's social attitudes. In the 1960s, you very rarely saw anybody with a disability out in public. People with disabilities stayed home to avoid people's stares, pointing, and comments. Those things are becoming politically incorrect now, which is good. With my disability, it was hard for people to realize my age, and they would often talk to me like I was a little kid. When I was 8 years old, I remember I was in the store and somebody pointed at me and said, "Look, there's a baby!" I looked at him, and said, "I'm not a baby; I have osteogenesis imperfecta #3," and he just walked off, stunned. My father laughed about that for about 20 years.

School was difficult. I couldn't play in sports and didn't go out on dates, things like that, so I began to feel a little funny about things. Though I won "Friendliest Boy in the Seventh Grade" and had friends, there were many times when I had to go off for operations. I'd miss classes, and I'd have accidents in school. Besides the physical pain, there's a lot of psychological pain, too, like having an accident in front of people. In junior high and high school, you don't want to look like that. That was hard. Accidents became more of a psychological problem than a physical problem for me.

Unfortunately, as I get older, the disability gets harder. Reality sets in: the reality of having to do things everyday, and learning how to do things differently, and having to be in a different social stratosphere. While other people are getting their own lives and families, I have to base my own lifestyle so much on my disability. My disability is always there to face. I have to think about it almost constantly. I have to be aware of what I'm doing and how I react to things, so I don't put myself in danger, and so that I can carry out daily functions. Many functions that people take for granted, I have to think out carefully. It frustrates me at times.

David Doostan

Mark Gash in front of his paintings

I have had a lot of problems with the medical profession. It was very difficult as a child to understand what was going on and the way I was treated. Groups of doctors would be hovering over me, yet they talked about me, never directly to me, so I began to feel like a specimen. There were many times when I was stripped naked without any regard for me.

Since they almost never saw someone with osteogenesis imperfecta #3, they showed me around like a stamp or coin or something they would collect. I understand that doctors have scientific curiosity and interest, but at the same time, I am a human—I'm not a stamp to be collected, even if my case is interesting. I really have no problem with people learning something through seeing me, but I do have a problem when there's a lack of respect, a lack of sensitivity to my humanness.

Even as I got older, there were times when my bones were broken, and I was still talked about like a specimen, never talked to directly. It makes me feel kind of funny, makes me feel like a child. Doctors were seen as authority figures by my parents, and so the doctors assumed greater authority. Doctors would say things in Latin or use medical terms, and my parents looked at me like they didn't know what was going on—that was very scary to me. But on many of those occasions, I would have had no reason to be scared if only the doctor had spoken in a way that we could understand.

I think that some doctors just see so many cases that they become insensitive to what they're really doing—working with a human being.

And doctors should realize that even though a disabled person's body may not be the same as another person's, they still need to respect that body. Undressing and staring at and speaking about and not directly talking to a disabled patient, even a child, hurts. Maybe the patients will not say anything but, really, it does affect their outlook on themselves for years to come.

Letter from the Southwest

Making our differences

Mark Carroll, Flagstaff, AZ, mcarroll@infomagic.com

Red and yellow signs for the reservation's crafts stand slow passing tourists like cultural speed bumps: *Chief Yellowhorse loves you. Don't miss Ol' Chief. Rugs, jewelry, pottery. Buy direct.* The boards after the stand continue: *Oops you missed us. Ol' Chief sez turn back now. Ice cold drinks. Friendly Indians behind you.*

The message offends. On many evenings while commuting home, I want to pull in, meet "Ol' Chief," and ask whether stereotype-swapping really sells arts and crafts.

We will not stereotype, we say. We will accept people on their own terms. Yet we struggle with the cultural collage that we encounter.

I never do. The line of RVs and out-of-state cars cooling in the volcanic gravel parking lot speaks for the power of his advertising.

Many non-Indian health professionals work on reservations because we seek a cross-cultural experience in caring. Some of us come to escape the money-driven, vapid-valued world of managed care; others are attracted to the open spaces, the rural calm. We uniformly arrive denying any internalized romanticizations of Native American life. We will not stereotype, we say. We will accept people on their own terms. Yet we struggle with the cultural collage that we encounter. Confusions prod us to generalize. We field questions from outsiders curious about Indian life, questions alternately fueled by reverent idealism and disillusioned cynicism.

"What are they really like?"

Visiting residents, medical students, and friends are sometimes schooled in the characteristic physical, spiritual, and cultural features that are "Navajo," in the similarities and differences between "Navajo"and "Hopi," and in the oft-discussed ways that Navajo and Hopi are unlike "Anglo." Although I don't remember ever leading such informal seminars myself, no doubt I have. The opportunity to wrap words around novel experiences is too appealing, the chance to sound expert on matters of culture and healing too alluring.

"Your work must be so rewarding."

My colleagues and I pretend that health care on the reservation is not so unusual. It is hard, however, to hide our conflicted feelings. We are proud to work where we do. We are also disappointed that the real world of the Native American is somewhat different from its idealized potential. Many tribal people suffer from diabetes, hypertension, and other chronic "lifestyle" diseases readily familiar to mainstream society. We know that these diseases are preventable; we do not know how to motivate Indian communities to prevent them. Reasons for change that work for one cultural vantage point do not easily convince people raised within another perspective.

Panos Pictures

"Two worlds," we sometimes respond. "Modern Indians live in two worlds."

We expect that each tribal member makes a solitary choice about who he or she is—culturally, socially—and then faithfully adheres to that choice, day in and day out.

But why only two worlds? Why not three, or four, or as many worlds as there are blends of tradition? All too often, "Western" professionals assume as I do that Indian people are either traditional or modern, in the same way that movie-educated tourists assume they are either friendly or hostile. We expect that each tribal member makes a solitary choice about who he or she is—culturally, socially—and then faithfully adheres to that choice, day in and day out. Is this how anyone, Navajo or Anglo, really lives? Personally, I don't like being called an Anglo. The label strips me of individuality. It restricts me of the freedom to change, the choice to be anything but what someone else thinks an Anglo should be. Why should I assume that a Navajo or Hopi would want the same limitation in potential? Why should I deprive anyone, no matter their cultural background, of the same fundamental right to shift and remold beliefs that I hold so precious for myself?

In the gathering zeal to cherish differences, perhaps, like "Ol' Chief," we rush too quickly to define those people we hope to know, undermining, as a direct consequence, the very principles we profess to embrace, the very diversity in healing we seek to protect.

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ANESTHESIOLOGY

NOVEMBER 5-7, 1999: **11th Annual Anesthesiology Update.** Monterey Plaza, Monterey, CA. Contact: (916) 734-5390.

NOVEMBER 4-6, 1999: **UC Otolaryngology Update: 1999.** UCSF at Ritz-Carlton Hotel, San Francisco, CA. 18.5 Cat I hrs. $425. Contact: (415) 476-5808.

CARDIOLOGY

OCTOBER 7-9, 1999: **23rd Annual Cardiology Update 1999.** American College of Cardiology at Carmel Valley Ranch Resort, Carmel, CA. 12 Cat. I hrs. Contact: Registration Secretary, Extramural Program Dept., American College of Cardiology; tel (800) 253-4636, ext. 695; fax (301) 897-9745.

OCTOBER 13-17, 1999: **Coronary Interventions 1999.** Scripps Clinic at Hilton La Jolla Torrey Pines, San Diego. Contact: Jill Hofmans, Conference Services Supervisor, Scripps Clinic. Dept. of Academic Affairs, 403C. 10666 N. Torrey Pines Rd., La Jolla, CA 92037; tel (619) 554-8556; fax (619) 554-6310.

OCTOBER 30, 1999: **Updae in Electrocardiography and Arrhythmia.** UCSF at Radisson Miyako Hotel, San Francisco, CA. 7.5 hrs Cat. 1. $195. Contact: UCSF Department of Medicine, CME, UCSF Box 0656, San Francisco, CA 94943-0656; (415) 476-5208.

DECEMBER 17-19, 1999: **Advances in Heart Disease.** American College of Cardiology at Grand Hyatt Hotel, San Francisco, CA. 16 hrs Cat 1. $490-565. Contact: ACC, Attn: EP, P.O. Box 7931, Baltimore, MD 21279-0231; (800) 253-4636, ext. 695.

DECEMBER 17-19, 1999: **The 16th Advances in Heart Disease.** San Francisco on Union Square, San Francisco, CA. 16 hrs Cat. 1. Contact: Registration Secretary, Extramural Programs Dept., 9111Old Georgetown Rd., Bethesda, MD 20814-1699; (800) 253-4636, ext. 695.

FEBRUARY 13-17, 2000: **International Congress 2000 on Endovascular Interventions.** The Phoenician Resort, Scottsdale, AZ . Contact: Erika Scott, 2632 N. 20th St., Phoenix, AZ 85006; tel (602) 266-2200; fax (602) 265-8885; escott@azheart.com.

EMERGENCY MEDICINE

AUGUST 16-19, 1999: **National Emergency Medicine Board Review.** American College of Emergency Physicians at Harrah's Las Vegas, NV. 40 hrs. $895. Contact: Center for Emergency Medical Education (800) 651-CEME (2363).

OCTOBER 3-5, 1999: **Northern California Trauma Center Conference.** UC Davis at Hyatt Regency, Sacramento. Contact: UC Davis; fax (916) 734-4298.

OCTOBER 7-9, 1999: **Pulmonary and Critical Care Medicine.** UCSF at Grand Hyatt Hotel, San Francisco, CA. 17 hrs Cat 1. $495. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656; (415) 476-5208.

OCTOBER 25-29, 1999: **Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco, CA. 32 hrs Cat 1. $675. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656; (415) 476-5208.

OCTOBER 28-31, 1999: **California Board Review.** A Comprehensive Review of Emergency Medicine. American College of Emergency Physicians at Paradise Point Resort, San Diego, CA. 50 hrs. $895. Contact: EMEDS; (888) 616-1711.

ENDOCRINOLOGY

OCTOBER 22-24, 1999: **Clinical Endocrinology for Primary Care Physicians.** Tropicana, Las Vegas, NV. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; tel (800) 421-3756; fax (303)798-5731.

NOTICE

State Associations should send their CME listings for publication to:

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WJM Western Journal of Medicine,
PO Box 7690, San Francisco, CA 94120-7690;
tel 415-974-5977; fax 415-882-3379;
wjmsf@pacbell.net.

ETHICS

SEPTEMBER 22-25, 1999: **Legal Issues in Damaged Brain Injury Cases.** UC Davis at Westin St. Francis Hotel, San Francisco, CA. Contact: UCD; (916) 734-5390.

FAMILY PRACTICE/PRIMARY CARE

AUGUST 20-22, 1999: **Primary Care Medicine.** Scripps Clinic at Coronaro Island Marriott Resort, San Diego. 16 hours. Contact: Cheryl Trinidad, conference Coordinator, Scripps Clinic, Dept. of Academic Affairs, 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037; tel (619) 554-8556; fax (619) 554-6310.

OCTOBER 2-4, 1999: **7th Annual Western Retreat: Practical Primary Care.** Scripps Clinic at Monterey Marriott. 12 hours. Contact: Cheryl Trinidad, conference Coordinator, Scripps Clinic, Dept. of Academic Affairs, 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037; tel (619) 554-8556; fax (619) 554-6310.

OCTOBER 22-24, 1999: **Clinical Endocrinology for Primary Care Physicians.** Medical Education Resources at the Tropicana Hotel in Las Vegas, NV. 11 hours. Contact: MER Linda Main, Meeting Coordinator, 1500 West Canal Ct., Ste. 500, Littleton, CO 80120-4569; (800) 421-3756.

OCTOBER 28-31, 1999: **11th Annual CME/Golf Meeting.** Nevada Academy of Family Physicians at The Orleans Hotel & Casino, Las Vegas, NV. Contact: Barbara Bolling, NAFP, P.O. Box 27713, Las Vegas, NV 89126-1713; (702) 228-5852; HYPERLINK mailto:nafplvbb@aol.com nafplvbb@aol.com.

DECEMBER 2-3, 1999: **Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco, CA. 13 hrs Cat 1. $370. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656; (415) 476-5208.

DECEMBER 10-12, 1999: **Issues in Women's Health.** Medical Education Resources at Tropicana Hotel, Las Vegas, NV. 11 hrs Cat 1. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; tel (800) 421-3756; fax (303)798-5731.

INFECTIOUS DISEASES

SEPTEMBER 29-OCTOBER 1, 1999: **Comprehensive Training in Sexually Transmitted Diseases.** California Department of Health at San Francisco. $50/day. Contact: California STD/HIV Prevention Training Center; (510) 883-6600.

DECEMBER 1, 1999: **AIDS-Associated Malignancies.** UCSF at Sheraton Palace Hotel, San Francisco, CA. 7 hrs Cat 1. $195. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656; (415) 476-5208.

DECEMBER 2-4, 1999: **Comprehensive Review of HIV Management—Winter.** UCSF at Sheraton Palace Hotel, San Francisco, CA. 24 hrs Cat 1. $455. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656; (415) 476-5208.

INTERNAL MEDICINE

AUGUST 22-27, 1999: **New Advances in Internal Medicine.** UC Davis at Embassy Suites, Monterey, CA. Contact: UCD; (916) 734-5390.

OB/GYN

SEPTEMBER 25-26, 1999: **Ultrasound Update: 1999.** Hilton Hotel, Sacramento, CA. (916) 734-5390.

DECEMBER 10-12, 1999: **Issues in Women's Health.** Tropicana, Las Vegas, NV. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; tel (800) 421-3756; fax (303)798-5731.

OCCUPATIONAL & ENVIRONMENTAL

SEPTEMBER 23-26, 1999: **Western Occupational Health Conference (WOHC).** American College of Occupational and Environmental Medicine and the Western Occupational and Environmental Medical Association at Monte Carlo Resort and Casino, Las Vegas, NV. 21 hours. Contact: Justine Abel, WOHC, 74 New Montgomery, Suite 230, San Francisco, CA 94105-3411; tel (415) 764-4083; fax (415) 764-4915; woema@hp-assoc.com; www.woema.com.

OCTOBER 4-8, 1999: **Occupational & Environmental Medicine IV.** UCSF at Radisson Miyako Hotel, San Francisco, CA. 40 hrs Cat 1. $750. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656; (415) 476-5208.

ONCOLOGY

SEPTEMBER 17-18, 1999: **5th Annual Cancer Research Symposium.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Contact: Office of CME, UC Davis Medical Center, 2315 Stockton Blvd., Camellia Cottage, Room 1019, Sacramento, CA 95817; tel (916) 734-5390; fax (916) 734-8966.

OCTOBER 14-16, 1999: **23rd Annual Physicians Cancer Symposium.** Scripps Health, Stevens Cancer Center, San Diego, CA at La Jolla Hyatt Regency Hotel. 16.5 CME hours. Contact: Ruthanne Crawford, Stevens Cancer Center, Scripps Memorial Hospital 9888 Genesee Avenue, La Jolla, CA 92037; tel (619) 626-6756; fax (619) 626-6793; racrawford@ch2.edu.

OCTOBER 14-16, 1999: **19th Annual Nurses Cancer Symposium.** Scripps Health, Stevens Cancer Center, San Diego, CA at La Jolla Hyatt Regency Hotel. 18 contact hours. Contact: Ruthanne Crawford, Stevens Cancer Center, Scripps Memorial Hospital 9888 Genesee Avenue, La Jolla, CA 92037; tel (619) 626-6756; fax (619) 626-6793; racrawford@ch2.edu.

OCTOBER 16, 1999: **Cancer 2000: Progress and Challenges.** Victor Valley Community Hospital at Victor Valley Community College, Victorville, CA. 8 hrs Cat 1. $90. Contact: Yvonne Newton, CTR, Victor Valley Community Hospital; (760) 245-8691, ext. 3542.

OTOLARYNGOLOGY

NOVEMBER 4-6, 1999: **Otolaryngology Update: 1999.** UCSF at Ritz-Carlton Hotel, San Francisco, CA. 18.5 hrs Cat. 1. $425. Contact: UCSF; (415) 476-5808.

PRIMARY CARE

OCTOBER 22-24, 1999. **Clinical Endocrinology for Primary Care Physicians.** Tropicana, Las Vegas, NV. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; tel (800) 421-3756; fax (303) 798-5731.

RADIOLOGY

SEPTEMBER 25-26, 1999: **Ultrasound Update: 1999.** UC Davis at Hilton Hotel, Sacramento, CA. Contact: UCD; (916) 734-5390.

RHEUMATOLOGY

SEPTEMBER 23-25, 1999: **Rheumatology Board Review.** UCSF at Radisson Miyako Hotel, San Francisco, CA. 20 hrs Cat. 1. $350. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656.

GENERAL/MULTIDISCIPLINARY

AUGUST 24-25, 1999: **BLS Instructor Course.** American Heart Association at San Leandro. 11 hrs. Contact: CPR Seminars; (925) 754-7900.

SEPTEMBER 22-23, 1999: **The Provider-Patient Relationship in the Context of the Hospitalist Movement.** 14 hrs Cat. 1. $350. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656.

SEPTEMBER 23-25, 1999: **Management of the Hospitalized Patient in the Managed Care Era.** UCSF at Cathedral Hill Hotel, San Francisco, CA. 20.5 hrs. $490. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656.

OCTOBER 15-17, 1999: **Physician Leadership Program.** California Academy of Family Physicians at Laurel Heights Conference Center, SF. 20 hrs. $1245-$1395. Contact: Laura Johnson Morasch; (415) 394-9121. Web: www.familydocs.org/ Orgs?hcli.html (e-mail: HYPERLINK mailto:HCLI@familydocs.org) HCLI@familydocs.org).

OCTOBER 21-22, 1999: **8th Symposium on Clinical Trials: Design, Methods and Controversies.** UCSF Laurel Heights Campus, San Francisco. 12 hrs Category I. $325 for physicians; $325 for nurses and allied health professionals; $150 for physicians in training. Contact: Registration office; (415) 502-1795.

OCTOBER 22, 1999: **Aesthetic Facial Surgery: The Evolution of Oculoplastics.** Renaissance Orlando Hotel, Orlando, FL. 6.75 hrs Cat 1. $400-450. Contact: Amy Wood, The Professional Image, Inc.; (949) 760-1522.

MARCH 2-4, 2000: **The Fifth International Conference on Continuous Renal Replacement Therapies.** Hotel Del Coronado, Coronado, CA. Contact: Shirley Kolkey, Complete Conference Management, 1660 Hotel Circle Noth, #$220, San Diego, CA 92108; tel (619) 299-6673; fax (619) 299-6675, c-c-m@worldnet.att.net.

GENERAL

OCTOBER 1-4, 1999: **Converse in Spanish.** Maricopa Health System at Scripps Memorial, San Diego; November 12-15, 1999 Glendale Adventist Medical Center 36 hrs. $695. Contact: Rios Associates; (619) 218-4875

OCTOBER 21-25, 1999: **Masters of Medicine 1999.** Continuing Medical Education Associates at Maui Marriott, Maui HI. 30 hours. $795. Contact: CMEA, P.O. Box 57072, Irvine, CA 92619-7072; tel (800) 447-4474 or (949) 250-1008; fax (949) 250-0445.

JUNE 22-23, JULY 10-11, SEPTEMBER 23, OCTOBER 11-12, NOVEMBER 9, 1999: **ACLS Provider/ renewal.** $115. For details: CPR Seminars; (925) 754-7900.

LOSS PREVENTION

SEPTEMBER 22-25, 1999: **Legal Issues in Damaged Brain Injury Cases.** Westin St. Francis Hotel, San Francisco, CA. Contact: (916) 734-5390.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, P.O. Box 7690, San Francisco 94120-7690; (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. CD ROM. $70. 2 hrs. Contact: Texas Medical Association; (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or phone (303) 377-1850. Brochures, course information, and registration forms are available from the contact person or organization.

TUESDAY NOON CONFERENCES: **Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline; (303) 425-2951.

FIRST WEDNESDAY OF EACH MONTH: **Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists; (303) 449-3566.

SECOND WEDNESDAY OF EACH MONTH: **Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell; (303) 629-3678.

CONTACT INFORMATION

U of Colo Contact—University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262; tel (303) 372-9050 or (800) 882-9153; fax (303) 372-9065.

IDAHO

To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701; (208) 336-2930. Brochures, course information, and registration forms are available from the contact person or organization.

JUNE 10-12, 1999: **22nd Annual Snake River Medical Forum.** St. Joseph Regional Medical Center at Red Lion Hotel, Lewiston, ID. Contact: Koleen Wagner; (208) 799-5460.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or phone (505) 828-0237.
NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

EVERY FIRST AND THIRD TUESDAY: **Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact: Thomas A. Naegele, DO; (505) 275-7267.

AUGUST 14, 1999: **Tenth Annual Update in Primary Care.** New Mexico Hispanic Medical Association at the Crowne Plaza Hotel, Albuquerque, NM. Contact: Kelly Little; tel (505) 828-0237; fax (505-828-0336.

OCTOBER 7-9, 1999: **Santa Fe Colloquium on Cardiovascular Therapy: Can Coronary Artery Disease be Stabilized or Reversed? What About Primary Prevention?** American College of Cardiology at Eldorado Hotel, Santa Fe, NM. 17 Cat I hrs. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology; tel (800) 253-4636, ext. 695; fax (301) 897-9745.

SATELLITE COURSES

Contact: Joe Treat or Jim Cato, Immunization Program; (505) 827-2366.
CONTACT INFORMATION
UNMSOM University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131; (505) 277-3942.

UTAH

All courses listed meet the criteria for Category 1 of the Physician's Recognition Award of the AMA. To list AMA Category 1 CME courses, send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address. NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

WEEKLY: **Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

WEEKLY: **Pediatric Grand Rounds.** Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION: CME HARBORVIEW Contact—Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA98104; (206) 223-5953. **PCMS CME Contact**—Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405; (206) 627-7137. **U/W (UNIVERSITY OF WASHINGTON) Contact**—U/W School of Medicine, Div. of CME, SC-50, Seattle, WA98195; (206) 543-1050. **VMMC (VIRGINIA MASON MEDICAL CENTER) Contact**—Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, POBox 900, Seattle, WA 98111; (206) 340-2058. **WSMA Washington State Medical Association,** Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121; (206) 441-9762.

WYOMING

All courses meet the criteria for Category 1 of the Physician's Recognition Award of the AMA. To list AMA Caegory 1 CME courses here, send information at least two months in advance to the Medical Education Committee, Wyoming Medical Society, P.O. B ox 4009, Cheyenne, WY 82009; email skeefe@wyomed.org; tel 307 634-2424; fax 307 632-1973.

AUGUST 30-SEPTEMBER 1, 1999: **Tutorial in the Tetons.** American College of Cardiology at Jackson Lake Lodge, Moran WY. 14.5 CME. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699; tel (800) 253-4636. ext. 695. fax: (301) 897-9745.

JULY 20-23, 1999: **Occupational and Environmental Medicine in Primary Care.** Rocky Mountain Center for Occupational and Environmental Health at Jackson Hole, WY. Contact: Registration Coordinator, The Rocky Mountain Center for Occupational and Environmental Health; (801) 581-5710.

OTHER CME OPPORTUNITIES: Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

SEPTEMBER 14-15, 1999: **Electronic Health Records in the Information Society.** Stockholm, Sweden. Contact: C. Peter Waegemann, Medical Records Institute. http://www.tepr.com.

SEPTEMBER 30- OCTOBER 2, 1999: **7th Annual Conference on Management of the Tinnitus Patient.** University of Iowa College of Medicine at Medical Alumni Auditorium, Room E331 UIHC, The University of Iowa Hospitals and Clinics, Iowa City, IA. Contact: Cheryl Schlote; tel (319) 384-9757; fax (319) 353-6739; cheryl-schlote@uiowa.edu.

Guidelines for Authors

Our readers represent all disciplines of medicine, but principally primary care physicians. We aim to publish manuscripts that are reliable and lively and that will improve the care of patients, the health of the public, or policies affecting either. Manuscripts should be of interest to a broad range of busy practitioners, physicians in training, and anyone who has an interest in quality health care. The purpose of a paper or letter may be to report, inform, alert, review, and discuss, but, above all, to teach. We aim to give quick and informative decisions on the articles we receive.

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WJM Western Journal of Medicine,
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San Francisco, CA 94120-7690;
wjmsf@pacbell.net.

Manuscripts may be submitted via e-mail, but must include print mail address and phone and fax numbers of the correspondent.

Manuscripts must be original, not previously published, and not under consideration by another publisher. If preliminary data were included in another presentation or publication, this should be noted in the cover letter and a copy of that publication should be included.

Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal). Research or project support should be included as a footnote to the manuscript and detailed in the Letter of Transmittal. Obtaining informed consent to protect patients' rights to privacy should be documented according to URM 1997.

All manuscripts should be double-spaced and, including references and abstract but not tables, should not exceed:

- **Original articles**: 2,500 words with a maximum of five tables and 30 references; structured abstract
- **Topics in Review**: 1,500 to 2,000 words with a maximum of 25 references; summary points†
- **Topics for Best Practice**: 2,000 words
- **Evidence-Based Case Reviews:** 2,500 words with two tables and/or figures; summary points†
- **Commentaries:** 600-800 words
- **Letters to the Editor:** 500 words

Structured abstracts

Manuscripts, except for case-based reviews, should include a structured abstract of no more than 250 words with the headings: objectives, design, setting, subjects, interventions, main outcome measures, results and conclusions.

Evidence-based case reviews

Interesting cases presented in an evidence-based, case-based review format provide readers with information and guidance with respect to clinically relevant choices made by practitioners—from diagnostic methods to conclusions as to what might have been done differently given the outcome. Topics to address include:

- epidemiology
- differences in demographic groups
- an evidence-based approach to diagnosis, management, and therapeutics; ethical issues
- cost/economic issues; when to involve a specialist
- what research is needed in the area.

Use of diagrams, tables, and algorithms is highly recommended. Authors should include 5-7 bulleted summary points for a busy primary care provider.

Letters to the editor

Letters must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review.

Letter of transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone and fax numbers included.

A letter of transmittal, except for one accompanying a manuscript from US government employees whose work was done as part of their official duties, must include:

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- a description of **sources of funding and the role of sponsors,** including their involvement, if any, in review and approval of the manuscript for publication.
- a statement of **financial disclosure:** "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed in the attached statement)."
- a statement that all human subjects involved in experimental investigation gave their **informed consent** and that approval was obtained from the appropriate institutional review board.

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- The original manuscript, two copies, and a copy of the manuscript (including references, tables, and figure legends) on disk (formatted for a PC/Windows platform and labeled with the word processing program used). Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides.
- Figures, black and white or color, in triplicate unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints (and transparencies for color figures) with the figure number, lead author's name, and top of the photo indicated with a label on the back.

WJM encourages the use of illustrations and asks authors to submit photographs for publication. When possible, patients should be asked to sign consent forms before pictures of them are published. This should be clearly stated and proof submitted with the manuscript. If obtaining consent is not possible, the reason should be stated in the cover letter. Changing the data on patients should not be used as a way of securing anonymity.

Figure legends, to be typed in sequence on the same page, should be in complete sentences. A letter of permission to borrow from the copyright holder (the previous publisher) must accompany any figures or tables previously published. The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

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A form for ordering reprints will be sent to the corresponding author when the article is published.

References

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Journal articles

Abbreviations of journal titles should conform to those used in Index Medicus. List up to three authors; for four or more, use et al. after listing the first three.

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996; 124:980-982.

Books

Ringsven MK, Bond D. Gerontology and Leadership Skills for Nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

Personal communications and unpublished data

The use of "personal communication" or "unpublished data" should be avoided and should not be included in the reference list.

For further information

Questions regarding the Guidelines for Authors may be directed to the Managing Editor in writing at the address above or by telephone 415-974-5977, fax 415-882-3379, or e-mail (wjmsf@pacbell.net).

Author checklist

- Original double-spaced manuscript and two copies, as well as PC-formatted disk.
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- A 250-word structured abstract.
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- Permission-to-borrow letters for any previously published illustrations or tables.
- Informed consent obtained.

Needlessly blind

David Heiden

This 6-year-old girl from Ethiopia went blind from vitamin A deficiency because she starved and was never immunized for measles.

David Heiden is an ophthalmologist practicing in San Francisco.

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Editor's pick

In 1994, the US Congress passed a law severely curtailing the powers of the Food and Drug Administration to regulate herbs and other alternative health products or dietary supplements. The law was in part a response to manufacturers, who urged deregulation to foster growth of their industry. (The manufacturers were no fools: the industry has tripled in economic terms since the law was passed.) But Congress was also responding to the passions of consumers who use alternative products on a regular basis. Many of these consumers have doctors.

But if we were to try and guess which of our patients are using alternative and complementary medicine, we might get it wrong. Adler (in a commentary on p. 158) suggests that common stereotypes about who's using alternative products are misleading. Research by Lee et al. underscores this point: although acupuncture is commonly thought of as an adult modality of care, Lee et al. found several pediatric acupuncturists in the Boston area who see an average of nine children per week.

What herbal products are people using, and is there any reliable evidence on the effectiveness and safety of these products? Overviews by Mar and Bent (p. 168), Gundling and Ernst (p. 191), Rotblatt (p. 172), Ko (p. 181), and Gunning (p. 198) show that there's more evidence on herbs than many of us think. More research evidence is needed, but we can expect that it will be forthcoming. Here again, passions have played a major role. In the early 1990s, Congress responded to the passions of those who sought further research on alternative medicine by establishing the Office of Alternative Medicine at the National Institutes of Health (NIH). By 1998, the office had gained sufficient credibility and following to rise in status to a National Center for Complementary and Alternative Medicine, with an appropriated budget of $50 million in fiscal year 1999. The center has its share of critics, but its role in funding and encouraging further study of herbs is crucial, given how many people are using such products.

—Michael S. Wilkes
—Miriam Shuchman

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Garlic

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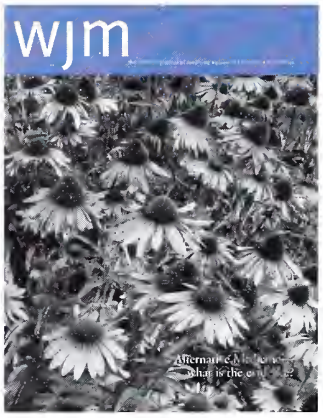

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Op-Ed

The principles and challenges of integrative medicine

More than a combination of traditional and alternative therapies

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Integrative medicine is a new term that sometimes is used interchangeably with complementary and alternative medicine, and at other times refers to treatments that combine conventional medicine and alternative modalities.[1] We define the fundamental principles of integrative medicine differently.

Central to our definition of integrative medicine is the body's innate ability to heal. Healing is believed to originate within the patient rather than the physician. For example, a patient presents with pneumococcal pneumonia and an antibiotic is prescribed. The patient recovers. Has the doctor cured the patient, the antibiotic eradicated the pneumonia, or the patient's immune system, assisted by the antibiotic's reduction of bacterial load, led to the patient's recovery? Integrative medicine asserts the latter.

Integrative medicine requires a shift from the "fixing" paradigm that has been central to biomedicine. When pathology is emphasized, the individual's experience of being ill and the social context of disease are neglected. Instead, an integrative medicine physician helps the patient consider the meaning of the illness for that patient, which can serve as a powerful agent for change and for healing. Language is used to support this natural tendency toward healing. A woman with metastatic lung cancer writes to her integrative medicine physician, "My body is falling apart…my spirit soars." Despite a low likelihood of cure, this woman articulates a healing process and sense of wholeness.

Sir William Osler's famous words—"It is much more important to know what sort of patient has a disease than what sort of disease a patient has"—express another principle of integrative medicine. Integrative medicine focuses on the needs of each individual human being, asking the questions, "What do you love? What gives you strength in times of trouble? What gives your life purpose or meaning?" Although not typical questions asked during a physician visit, these questions are essential in integrative medicine, because they allow providers to understand their patients' values and the context in which they live. It is then possible to design a unique treatment plan.

The principles of integrative medicine maintain that the experience of a therapeutic relationship facilitates the healing process. The physician emphasizes the patient's participation and responsibility and recognizes the patient's preferences and self-knowledge when designing a treatment plan.

Integrative medicine focuses on prevention as a means of enhancing health and well-being. Five areas of prevention are addressed: physical activity, nutrition, screening, stress management, and spirituality. The first three are commonly stressed by traditional physicians, but often without specific recommendations.[2] For example, the relationship between diet and certain chronic diseases is often not addressed. Physicians who practice integrative medicine are encouraged to inquire about patients' sources of stress and coping strategies. Regular practice of relaxation such as t'ai chi or meditation are recommended to patients, as are breathing exercises and self-hypnosis. Physicians inquire about the patient's spiritual life, because they consider understanding this aspect of patients' lives as critical to promoting health.

Complementary and alternative medicine serves an important role in integrative medicine, yet the two are not synonymous. The former opens new paradigms for many conventionally trained physicians; for example, explaining the Chinese medical system's use of moxibustion to turn a breech baby.[3] The latter is committed to the practice of good medicine whether its origins are conventional or alternative[4]; for example, offering adaptogens for replenishing the qi, mind-body, as well as nutritional recommendations to patients with "fatigue," when the lack of a clear diagnosis may not lead an allopathic physician to offer treatment. Complementary and alternative medicine assists the practitioner of integrative medicine in taking a holistic approach.

Although centers of integrative medicine have opened in many cities, little has been written about how complementary and alternative medicine and allopathic providers collaborate to provide care.[5] Getting to know patients takes time; in the old general practice model, physicians had a lifetime in which to get to know their patients. Today's mobile society, as well as economic incentives in our current healthcare systems, do not support this time investment. Finally, it is unclear how evidence-based medicine should be applied to integrative medicine, when the field stresses individual treatments and is willing at times of low risk to use unproven treatments.

Integrative medicine shifts the paradigm from sickness to health, keeps the patient in the central focus of care, and multiplies the number of strategies available to the patient. It is a new kind of medicine that shifts the experience for both patient and provider.

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Complementary and alternative medicine needs an evidence base before regulation

Why train practitioners in therapies that do not work?

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Complementary and alternative medicine is practiced by both physicians and nonphysicians—by far more nondoctors than physicians in most countries. Physicians may employ acupuncture, hypnosis, biofeedback, or any of the other modalities of complementary and alternative medicine. Osteopathic doctors in the United States learn spinal manipulation in their training, although many later choose to make little use of it in routine practice.[1] Chiropractors are licensed in every state of the United States, acupuncturists licensed or certified in 32 states and the District of Columbia, massage therapists in 25 states, and naturopaths in 11 states. Homeopathy is separately licensed only in Arizona, Nevada, and Connecticut, although other states may include homeopathy in the scope of practice of naturopaths, chiropractors, or oriental medicine practitioners. Herbalism is not separately licensed or certified, but it is considered within the scope of practice of naturopaths, acupuncturists, or chiropractors in some states. There are no separate licensing or certification standards for other complementary and alternative medicine practices.

In the United Kingdom, complementary and alternative medicine (with the exception of homeopathy) is almost entirely in the hands of therapists without medical qualifications. The number of these therapists is now estimated to equal that of primary care physicians. Since it was established in 1948, the British National Health System has incorporated homeopathy; it still operates five homeopathic hospitals, run by physicians. There are neither statutory regulations nor minimal educational requirements for practitioners of complementary and alternative medicine in the United Kingdom. Laudable initiatives, however, are about to change this situation for osteopathy and chiropractic.[2]

What do we know about practitioners of complementary and alternative medicine? Generally they are sincere people, dedicated to helping patients. Yet cynics would probably point out that sincerity renders a quack only more dangerous to the public. A large proportion of these practitioners subscribe to holistic worldviews and have relatively little regard for or knowledge of science.[3] Most earn only a modest income.[4] Practitioners tend to work in small, often single-handed practices, and their referral rates to physicians are low.[5] They spend long periods of time with patients and there is evidence (albeit inconclusive) to suggest that they often develop better therapeutic relationships with their patients than do physicians.[6] In the United Kingdom, most practitioners of complementary and alternative medicine say they would like to practice more extensively within the regular health services[7] but, due to their relatively long consultation times and hence high costs per patient, it is doubtful whether their services will prove to be affordable.[8] Complementary and alternative medicine might therefore continue to be mostly private medicine.

Practitioners' training in complementary and alternative medicine is highly variable. Most have benefited from some formal training,[8] but many physicians still worry about their medical competence. The degree of competence required to guarantee patients' safety varies for obvious reasons. It is necessarily high when therapies associated with potentially serious adverse effects are being administered, such as spinal manipulation, acupuncture, or herbal treatments.

While regulation and training are to be applauded, establishing an evidence base must logically precede regulation of the practice of complementary and alternative medicine. If, for instance, iridologists would regulate all aspects of their profession, including rigorous training in the art of iridology, this would not change the science, which shows that this diagnostic technique is not valid.[9]

It follows that an evidence base in complementary and alternative medicine must be established and used to guard against institutionalizing mere assertions. Of course, regulating existing practice is better than doing nothing, but without a solid evidence base, the regulation of practitioners serves little purpose. These are not academic issues but determinants of patients' safety, and addressing these issues unemotionally will, in the long term, help the emerging field of complementary and alternative medicine.

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Why are children with cancer being exposed to complementary medicine?

Untested therapies are not the best choice in the face of deadly disease

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Studies suggest that up to 40% of adults in North America use or have used alternative therapies.[1-3] This percentage may be equally high for children.[4] While the use of such therapies among adult cancer patients has been studied reasonably well,[5] few studies have examined their use in children with cancer. One of these, the only population-based survey, showed that 42% of respondents had used alternative therapies.[6] It is clear that children with cancer are increasingly being exposed to alternative therapies. While some of these therapies may have benefits, or at least may not cause harm, there are concerns among practitioners in the field of pediatric oncology regarding their use in children with cancer, in particular where alternative therapies are elected over conventional and evidence-based therapy.

The use of clinical trials for children with cancer has resulted in astounding progress during the last three decades.[7,8] Conventional cancer treatments are therefore only recommended after formal scientific study of their safety, tolerability, and efficacy. We have previously expressed our inability to understand how conventional childhood cancer treatments occasionally are repudiated in favor of alternative approaches that lack any evidence of efficacy.[9] A recent example of such an incomprehensible choice, which received extensive media attention in Canada, involved a 13-year-old boy with localized osteogenic sarcoma. After initial treatment, he refused further chemotherapy and amputation, opting for herbal and alternative remedies. The expected five-year event-free survival for non-metastatic osteogenic sarcoma, following treatment through conventional therapies, is approximately 65%.[10] Yet, despite this promising outlook, this boy and his parents expressed more faith in alternative therapy. Saskatchewan's Ministry of Social Services tried to take legal charge of his medical care, but subsequently dropped the case after doctors reported the cancer had spread to the lungs. The boy's parents ended up taking their son to an alternative treatment clinic in Tijuana, Mexico. He died in June, less than a year after his diagnosis.

What can be the rationale for the apparently increasing confidence in unproven therapies for the treatment of deadly disorders? In our view, there are clear causes underlying the dramatic increase in interest in alternative therapies. An awareness of these three forces seems to us to constitute the first step toward addressing the dilemma. Sampson[11] has proposed that cultural relativism and postmodernist deconstruction might have provided the impetus to an antiscientific culture in which alternative medicines have flourished. Both doctrines have given rise to a view toward "value free" analysis, which concludes that "science has validity [only] within the community accepting its point of view, without necessarily being more valid than pseudoscience." This leads logically, in Sampson's argument, to the belief that "there is not necessarily any validity at all to the scientific view, which is taken to represent the prejudices of a system dominated by European males."

Clearly the public has become increasingly suspicious of the sciences, and the biomedical sciences in particular. This view has led patients to question our motives in presenting data in support of or against therapeutic options. They have couched their suspicions in terms of holistic concerns, efforts to address the mind and spirit as well as the body or, occasionally, as fairly fundamental interpretations of religious doctrine. In any case, rebuttals to their concerns are seldom successful, and often lead to an amplification of their suspicions.

Unfortunately, it appears that not all therapeutic approaches are held to equal standards.

Our society—rightfully so—expects pediatric oncologists to discuss planned therapeutic approaches with parents and patients in *exacting* detail and with some form of statistical representation of their risks and opportunities for success. While arguments can be made for the avoidance of precise numerical data regarding risk or prognosis, patients invariably ask for this information. Where numbers are avoided, the sheer volume of information derived from countless risk and efficacy studies is often frightening to patients, encouraging them to examine alternatives that appear less threatening. It is our obligation, however, to provide accurate, precise information in comprehensible form to our patients. Obtaining truly informed consent for any therapeutic intervention demonstrates respect for the patient and acknowledges the importance of his or her decision. It is essential that the nature of the treatment, as well as the known risks and benefits, be disclosed to the decision maker(s).

Unfortunately, it appears that not all therapeutic approaches are held to equal standards in this regard. Proponents of many of the alternative therapies have argued that their methods and materials cannot be subjected to the rigors of the scientific method. They tend to provide information about side effects, mechanisms, and outcomes in terms of vague or anecdotal findings, if they report such information at all.

When patients are desperately seeking treatment for themselves or, worse, when parents seek options for their children, they will cling to any statement that offers hope. The accuracy of the data underlying evidence-based therapies is frightening to patients, and contrasts poorly with the less precise—but less frightening—information provided about most alternative therapies. Many patients are likely to regard "absence of evidence of serious side effects" as equivalent to "evidence of absence." It is not surprising, therefore, that when learning of various alternative therapies, patients might view those treatments in a more favorable light, seeing them to hold more potential than is warranted by the evidence.

Finally, human beings need to maintain hope. Loss of hope creates despondency or desperation. Patients' or their parents' efforts to find "alternative" therapies are often a reflection of their desperation and their need to regain some sense of control in the face of proffered therapies, which appear to threaten their control over life and their hope against death.

It is imperative that the evidence underlying conventional therapies be provided in an honest manner, but one that allows the patient or parent to maintain hopefulness. Approaches that seem to threaten their need to control or their desire for hope raise the probability that they will be driven by desperation to seek alternative therapeutic options.

Patients cannot and should not be denied freedom of choice. But as a society, and as healthcare professionals, we have the obligation to ensure that the information necessary to make an informed choice is available. The necessity for such information applies to alternative therapies, as it does to conventionally based therapies. Society must, therefore, insist that our governments formulate expectations for these alternative therapies and their practitioners, just as expectations are rightfully held for evidence-based therapies and theirs.

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Mail

Hypertension in mother and baby linked to ingestion of Chinese herbal medicine

To the Editors,

Dong quai is a popular Chinese herbal medicine. In China, it is prepared as a soup, with half-dollar–sized pieces of thinly cut, dried root of *Angelica sinensis* added to chicken stock. In the United States, dong quai is sold as a powder contained in capsules. It is among the 20 top-selling herbal medicines.[1] It is taken by women as palliation for dysmenorrhea, irregular menstruation, anemia, postpartum weakness, and uterine hypotonia. Some doctors also prescribe dong quai for premenstrual syndrome and menopausal symptoms. We report a possible association of dong quai with hypertension in a mother and her breast-fed infant. We are unaware of any such association having been reported previously.

A 32-year-old woman of Chinese-Malaysian origin, 3 weeks postpartum, was treated in our emergency department (ED) for the acute onset of headaches, weakness, lightheadedness, and vomiting. Her blood pressure in the ED was 195/85 mm Hg, repeated several times. Review of her medical records revealed that she had been normotensive and normoglycemic during her uneventful term delivery.

The patient stated that she had ingested a special ethnic soup prepared by her mother, who had recently arrived from Malaysia to help with postpartum chores. The soup had been made with pieces of the dong quai root *(Angelica sinensis)* purchased in Malaysia. The patient denied taking other medicinals or herbal remedies. She said she had ingested dong quai soup twice on the day she presented in the ED, although we were not able to assess the dosage of dong quai in the soup nor could we learn if her ingestion represented a possible overdose. Her ED evaluation including blood chemistry panels and CT of the head was normal. She improved rapidly and was normotensive within 12 hours.

The next day, her 3-week-old son was taken to his pediatrician for evaluation for possible hypertension. The infant's blood pressure was 115/69 and 117/63 in the left leg and arm, respectively (90th centile for age is 106/65). The elevated blood pressure was confirmed by successive Dynamapp™ readings over 30 minutes. The baby was not treated with antihypertensive medication, and his pressure normalized within 48 hours. During that time, breastfeeding was temporarily withheld.

A possible explanation for hypertension in this woman and her child is an adverse effect of dong quai soup, passed to the child in the breast milk. We could not confirm this explanation because we were unable to obtain a sample of the soup for toxicological analysis. Pieces of the dong quai root purchased in Malaysia in the same herbal medicine shop were obtained, however, and were identified as true dong quai by an expert in Chinese herbal medicine. In addition, toxicological analysis of samples of sliced, dried dong quai root, purchased from a Chinese herbal pharmacy in San Francisco, and of granular dong quai root in capsule form, purchased in a pharmacy (Nature's Way, 565 mg/capsule), showed no analytic differences between the root and the capsular product.

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Original Research

Survey of acupuncturists: practice characteristics and pediatric care

ABSTRACT ● **Objective** To describe the practice characteristics and pediatric care provided by licensed acupuncturists. ● **Design** Cross-sectional survey. ● **Setting** Boston metropolitan area. ● **Subjects** 227 licensed acupuncturists were surveyed; 140 (62%) responded. ● **Main outcome measures** (1) Demographics, (2) practice characteristics, (3) pediatric care, (4) recommendations of peers recognized as experts in pediatric acupuncture. ● **Results** (1) Demographics: 70% Caucasian, 61% female; (2) practice characteristics: average of 39 visits weekly with an average charge of $54 for a 57-minute visit; patients were typically scheduled for follow-up once or twice weekly; only 5% of fees were covered by insurance; 80% recommended herbal remedies and 66% dispensed herbs in the office; (3) few acupuncturists treated more than one child per week; most used non-needle techniques or Japanese-style acupuncture to stimulate points in children; 85% would refer a febrile two-week-old infant immediately to a physician; (4) only 17 acupuncturists were recommended by three or more peers and saw three or more patients weekly; their practices were all in wealthy suburban areas. ● **Conclusions** Most acupuncturists in the Boston area are Caucasian and female. Compared with physicians, they schedule patients for more frequent follow-up, allocate more time, are less likely to be reimbursed by insurance, and treat fewer children. Additional studies are needed to assess effectiveness, quality, and access to acupuncture services for adults and children.

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Introduction

Complementary and alternative medical therapies are rapidly becoming more mainstream. The proportion of Americans using unconventional medicine increased from 34% in 1990 to 42% in 1997, with a 45% increase in expenditures on alternative medical professional services during the same period.[1-4] In 1992, 11% of Canadian children consulted an alternative medicine practitioner.[5] Among children with chronic or debilitating conditions, such as cystic fibrosis, juvenile rheumatoid arthritis, and cancer, utilization of complementary and alternative medicine ranges from 31% to 70%.[6-11]

Increasing numbers of primary care physicians are interested in, personally use, and refer patients to complementary and alternative medicine providers. A majority of American, British, and Dutch physicians consider alternative therapies (such as acupuncture) effective, legitimate medical practice[12-14] and express interest in training for complementary and alternative medicine.[12,15-17] Twelve to 30 percent of general practitioners in England, Australia, and New Zealand incorporate alternative therapies into their own practices.[13,15,18,19] More than half of physicians surveyed in the United States, Canada, Israel, and England reported recommending alternative therapies to their patients.[12,15,20,21]

Acupuncture is commonly used by adults and children[3-5] and is the complementary and alternative medicine therapy most frequently recommended by physicians.[13,16,21,22] A National Institutes of Health (NIH) consensus conference concluded that acupuncture is effective in reducing adult postoperative and chemotherapy-associated nausea and vomiting and postoperative dental pain.[23] Promising results exist for acupuncture in treating headache,[24-26] dysmenorrhea,[27] and neck pain.[28] As of late 1998, one third of pediatric pain clinics in North America offered acupuncture services for pain management.[29] Millions of Americans have tried acupuncture.[30] The number of graduates from American acupuncture schools doubled between 1992 and 1997.[31] As of 1998, there were approximately 11,000 practicing acupuncturists in the United States; that number is expected to reach 21,000 by 2005.[30,31]

Given the increasing public and medical interest in alternative medicine, it is likely that physicians will be asked more often to refer patients to and coordinate services with complementary and alternative medicine providers. As we inaugurated the Center for Holistic Pediatric Education and Research, we received requests from pediatricians at the hospital and in the community, asking for a referral list of reputable complementary and alternative medicine providers for children. Rather than choosing one or two practitioners via word-of-mouth referrals, we wanted to identify all local acupuncturists and describe the following characteristics: (1) demographics of acupuncturists; (2) practice characteristics, including visit length and frequency, fees, and insur-

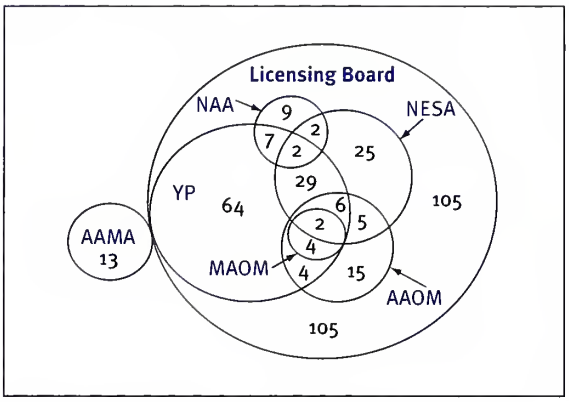

Figure 1 *This Venn diagram depicts the identification of licensed acupuncturists in the Boston metropolitan area from the following sources: AAMA = American Association of Medical Acupuncture (n = 13); NAA = National Acupuncture Alliance (n = 20); NESA = New England School of Acupuncture (n = 71); AAOM = American Association of Oriental Medicine (n = 36); MAOM = Massachusetts Association of Oriental Medicine (n = 6); YP = Yellow Pages (n = 118); Licensing Board (n = 279).*

ance reimbursement; (3) pediatric care, including training, techniques, and specialization; and (4) peer recommendation of providers.

Methods

To answer these questions, we performed a cross-sectional survey of acupuncturists in the Boston metropolitan area from July to October 1998. Subjects were eligible if their practice was located in the Boston metropolitan area as defined by the National Census Bureau.

Nine data sources were used to attempt to identify practicing acupuncturists: the Greater Boston Area yellow pages, the Commonwealth of Massachusetts Board of Registration in Medicine, the National Acupuncture and Oriental Medicine Alliance, the American Association for Oriental Medicine (AAOM), the American Association for Medical Acupuncture (AAMA), the American Oriental Bodywork Therapy Association (AOBTA), the Massachusetts Association of Acupuncture and Oriental Medicine (MAAOM), the Massachusetts Acupuncture Society, and the New England School of Acupuncture (NESA). Subjects were included if they were listed on one or more of the above data sources or if they were identified by another acupuncturist during the course of the study. The total number of acupuncturists identified in the greater Boston area, after eliminating overlapping memberships, was 295 individuals (Figure 1).

The survey was based on questions from the National Ambulatory Medical Care Survey and developed in collaboration with a licensed acupuncturist (ESH). It was pilot-tested through a telephone survey of a subset of 45 acupuncturists listed in the yellow pages. Questions were refined, and from the remaining lists, 195 acupuncture practices were chosen by computer randomization to receive written surveys by mail in July 1998. Thirteen addresses were nondeliverable. Nonrespondents received second surveys by mail and a follow-up telephone call. Of the 227 acupuncture practices surveyed, 140 (62%) acupuncturists completed and returned surveys. Reasons for nonresponse included lack of interest in the study, poor English comprehension or speaking abilities, little experience with children, and being "too busy."

The self-administered survey contained four pages of questions and required 10 minutes to complete. Demographic items included age, race, and sex. Six questions addressed professional status and training: educational degrees, acupuncture school, special training in pediatrics, year of graduation from acupuncture school, year of licensing in Massachusetts, and membership in professional societies. Four questions addressed acupuncture techniques, including the style of acupuncture performed, the use of herbal remedies, and the use of special techniques for children. Nine questions addressed practice patterns: solo versus group practice, number of patients seen per week, number of pediatric patients (<21 years old) seen per week, length of initial and follow-up visits, and frequency of visits. Fee and insurance issues were addressed in six questions: initial/follow-up visit fees, the proportion of patient fees covered by fee-for-service insurance, the use of a sliding scale, acceptance of Medicaid patients, and participation in HMOs and other insurance plans. To assess practitioners' clinical judgment and approach to pediatric care, acupuncturists were asked what actions they would take if presented with a 2-week-old infant with a fever of 101.5 °F.

Acupuncturists were asked to whom they would refer a pediatric patient for acupuncture treatment if they themselves were unable to provide treatment. This question was aimed at developing a peer referral list of pediatric acupuncturists. Our a priori criteria for this list included (a) caring for at least three pediatric patients per week; (b) referral by at least three other acupuncturists; (c) willingness to accept referrals from the Children's Hospital; and (d) state licensure.

All data were entered into Microsoft Access, exported to Microsoft Excel, and analyzed using simple descriptive statistics. Normally distributed data are reported as averages; non-normally distributed data are reported as medians, modes, and ranges. Because there were no a priori hypotheses and a small sample, no comparative statistical tests were performed.

Results

The vast majority of acupuncturists (279/295 = 95%) were identified through the Massachusetts Board of Registration in Medicine. Only 41% of acupuncturists were listed in the yellow pages (Figure 1). Because licensure is not

required for physicians to practice acupuncture in Massachusetts, none of the physician-acupuncturists were on the list provided by the Board of Registration in Medicine. Only three (of 13) physician-acupuncturists were listed in the yellow pages.

Most (61%) respondents were female. The average age was 44 (± 7) years old. Seventy percent identified themselves as Caucasian; 29% as Asian; 1% as African American. Thirteen percent were licensed medical doctors or nurses.

The vast majority (68%) of respondents were trained in the United States. For example, 60% received their formal training at the nearby New England School of Acupuncture (NESA); 23% had trained in China and the remaining 9% in other countries, including Japan, South Korea, England, and Russia. Half of the respondents reported receiving specific training in treating pediatric patients, ranging from postgraduate weekend seminars to clinical training during acupuncture school.

Slightly more than half (51%) of respondents were in solo practice (Table 1). Respondents saw an average of 39 patients per week (range: 2-150), with patients typically returning once or twice a week.

Visit lengths averaged 80 minutes for initial visits and 57 minutes for follow-up visits; charges averaged $78 for initial and $54 for follow-up visits (Table 1). Only 5% of fees were covered by insurance, and these tended to be worker's compensation or automobile accident claims. Most practitioners (64%) offered sliding scales, but only 21% saw Medicaid patients.

Acupuncture and herbal medicine are both intrinsic aspects of traditional Chinese medicine. Most (80%) respondents prescribed herbal remedies, and 66% dispensed herbs within their office. Forty-two percent practiced Chinese acupuncture; 43% practiced a combination of Chinese and Japanese acupuncture; 8% practiced Japanese-style acupuncture; and 8% practiced other styles, such as Korean or European.

Few acupuncturists regularly cared for children. Those who did used a variety of non-needle techniques to stimulate acupuncture points: (1) moxa (74%), a Chinese herb (mugwort) burned to generate heat; (2) magnets (56%); (3) massage (55%); (4) electrical stimulation (41%); (5) *shoni shin* (24%), the Japanese system of stimulating acupuncture points with small tools—round-edged rakes, tapping needles, press needles—instead of needles; and (6) plum blossom hammer (24%), a light hammer with nine thin, short needles, used to tap the skin at acupuncture points.

Presented with the hypothetical case of a febrile neonate, 85% of the nonphysician acupuncturists reported that they would directly refer the patient to a medical doctor or the emergency room. The remainder would either take more history (9%) or treat the patient immediately (6%).

Table 1 *Practice characteristics of acupuncturists*

Characteristics	Statistics
Type of practice	49% Group
Number of patients/week	39±24*
Visit length (minutes)	
Initial visit	80±21*
Follow-up	57±12*
Visit fees	
Initial visit	$78±37*
Follow-up	$54±14*
Percentage of patients covered by insurance	5%†, 0%‡, 0-100%¶
Percentage with sliding scale	64%
Percentage accepting Medicaid patients	21%

* Mean ± standard deviation; † Median; ‡ Mode; ¶ Range

Table 2 *Characteristics of 17 peer-recommended pediatric acupuncturists versus others*

	Pediatric acupuncturists (n = 17)	Others (n = 123)
Percentage with pediatric training	53%	50%
Average number of patients/week	58±35*	36±21
Pediatric patients per week	9§; 7†; 10‡	2; 1; 0
Percentage offering sliding scale	35%	65%
Percentage seeing Medicaid patients	35%	20%
Style of acupuncture	35% Japanese 29% Chinese 18% Chinese+Japanese 18% Korean	3% Japanese 43% Chinese 46% Chinese+Japanese 8% Other

* Mean ± standard deviation; § Mean; † Median; ‡ Mode

Nine respondents were physicians. Anesthesia was their most common specialty. They saw an average of 26 acupuncture patients weekly. For initial and follow-up visits, consultations lasted an average of 68 minutes and 37 minutes respectively; fees averaged $154 and $75 respectively. One third of patient fees were covered by insurance. Forty-four percent of medical acupuncturists offered a sliding scale; 56% saw Medicaid patients. Among just the physician-acupuncturists, one third reported practicing French acupuncture, one third Japanese, and 22% Chinese-style. Twenty-two percent prescribed and dispensed herbs.

Seventeen acupuncturists met our a priori criteria for inclusion on our pediatric referral list and are hereafter referred to as the "pediatric acupuncturists" (Table 2). Two were physician-acupuncturists. Half reported spe-

cial pediatric training. All of the practices were located in Boston's wealthier suburbs. They saw an average of 58 patients weekly, including an average of nine pediatric patients. Only 35% of this group offered a sliding scale and 35% accepted Medicaid patients. Many practiced special, gentle needle techniques, particularly Japanese (35%) or Korean-style (18%) acupuncture. Eighty-two percent reported using special non-needle techniques for treating children, including moxa (88%), magnets (76%), massage (53%), shoni shin (29%), plum blossom hammer (18%), and toyo hari (18%).

Discussion

This is the first study to address the practice characteristics and pediatric care provided by licensed acupuncturists in the United States. The major purpose of this study was to describe: (1) the demographic characteristics of American acupuncturists; (2) their practice characteristics, including visit length, frequency, fees, and insurance reimbursement; and (3) pediatric care by acupuncturists, including training, techniques, and specialization.

In Massachusetts (and other states that require licensure for nonphysicians to practice acupuncture), the most efficient method of identifying acupuncturists is to contact the state Board of Registration/Licensure for names of licensed (nonphysician) practitioners and the American Association for Medical Acupuncture (AAMA) for names of physician-acupuncturists. Other sources, like the yellow pages, yielded fewer than half of the licensed providers. The proposed method does not identify unlicensed acupuncturists practicing within a family lineage or those not accredited by the licensing board, however.[32]

Insufficient physician contact time, provider accessibility, and more personalized attention are significant reasons that patients seek alternative therapies.[5,33,34] In our sample, acupuncturists typically saw patients once or twice weekly and visits lasted from 50 to 90 minutes. The frequency and duration of acupuncture sessions are substantially greater than office visits to mainstream physicians.[35] Although many acupuncturists see several patients simultaneously, the longer total visit length and higher frequency of treatments might contribute to patients' perceptions that they are receiving more personal attention and care.

Fees for acupuncture services are comparable to office visit fees for physicians.[36] However, almost all (95% median) acupuncture fees are paid by patients out-of-pocket. Total acupuncture costs per patient may also be higher, due to more frequent office visits. A majority of acupuncturists (65%) offer sliding scales for patients, while fewer physician-acupuncturists (44%) and pediatric acupuncturists (35%) offered reduced rates. Because current Medicaid policy does not cover acupuncture services, few acupuncturists saw Medicaid patients (21%), although more physician (56%) and pediatric (35%) acupuncturists did. Physician-acupuncturists' fees appear to be somewhat higher, but this increase is offset by higher insurance reimbursement rates. With current insurance and Medicaid reimbursement rates, acupuncture services may be limited to affluent families.

Acupuncturists were willing to identify peers who specialize in pediatric care. Although this might not be the optimal way to develop a referral network, we currently have no other way of identifying complementary and alternative medicine practitioners who treat children and who are both experienced and respected by their peers. This kind of peer referral does not and cannot answer questions about the effectiveness or safety of acupuncture in treating any particular child or condition, but it can provide a potential network of collaborating clinicians for research studies to address these important clinical questions.

In the United States, where the concept of therapeutic needling is not a common cultural tradition, many children may be wary of acupuncture treatment. Only a minority of respondents cared for more than one pediatric patient per week. Seventeen of 295 acupuncturists met our a priori criteria for pediatric acupuncturists. Most of them reported using gentler or noninvasive techniques to stimulate acupuncture points. Magnets, press balls, indirect moxa, and tiger warmer, a warming skin salve, are all superficial devices that stimulate acupuncture points and energy flow without penetrating the skin. These might be considered "pediatric" acupuncture techniques, because they are less threatening to children than needles.

This study has several limitations. First, it was confined to the Boston area. It needs to be replicated in other areas, particularly those without acupuncture schools. Second, since all telephone and written surveys were in English and directed at licensed providers, non–English-speaking acupuncturists and nonlicensed acupuncturists were underrepresented. The selection against non–English-speaking acupuncturists could neglect an important sector of practicing acupuncturists. Alternately, this self deselection might be useful with respect to clinical referrals if these acupuncturists are not officially licensed or unable to communicate with physicians, children, and parents. Third, the busier acupuncture practices may have been underrepresented. Since one of the criteria for the selection of pediatric acupuncturists was three or more peer recommendations, those teaching at the nearby acupuncture school had the advantage of greater exposure within the local

acupuncture community. Of the peer-recommended pediatric acupuncturists, for instance, 61% were instructors at NESA.

Other limitations include the self-reporting of data as opposed to observational reporting. This descriptive survey of practitioners also does not address patient satisfaction, efficacy, or side effects of acupuncture treatment.

Despite these limitations, this study provides the first systematic description of American acupuncturists, their practice characteristics, and pediatric care. Most are female and white. Frequent and long visits may contribute to patient satisfaction. Low rates of insurance coverage may limit availability of services, however. Pediatric care is specialized and often incorporates non-needle techniques. Very few acupuncturists (5%) treat significant numbers of children.

Given the growing use of complementary and alternative therapies and the increase in patient requests for alternative medicine referrals, additional studies are needed to assess the characteristics, availability, costs, and effectiveness of acupuncture and other complementary and alternative medicine services for adults and children nationally.

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COMMENTARY

Pediatric complementary and alternative medicine use: physician-patient communication is vital

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Increasing numbers of Americans are using complementary and alternative medicine for themselves and their children. In a recently published research agenda for pediatrics, Kemper, Cassileth, and Ferris[1] describe the urgent need for research on the use of these treatments in children. Top priorities include clinical research on the effectiveness and safety of complementary and alternative medicine therapies and qualitative research on the consequences that diverse explanatory models of health and illness will have on patient-provider communication, adherence to professional recommendations, and satisfaction with care. As Lee, Highfield, Berde, and Kemper note in their survey of licensed acupuncturists in the Boston metropolitan area, little is known about pediatric complementary and alternative medicine usage, even for common modalities such as acupuncture.

The overwhelming majority of adult complementary and alternative medicine users in the United States also use biomedicine, either concurrently or serially, but most patients do not tell their physicians about their complementary and alternative medicine use.[2] This situation heightens the importance of physicians' awareness of patients' health-related beliefs and practices. Certain complementary and alternative medicine therapies have demonstrable beneficial effects; some can be harmful under certain conditions; others may interact with pharmacologic therapies in clinically significant ways. Findings from a population-based, prospective cohort study indicate that only 54 % of study participants who used complementary and alternative medicine disclosed their use to their physicians, while 94 % discussed details of their biomedical treatments with their alternative practitioner.[3] In other words, information regarding patients' complementary and alternative medicine use is more poorly integrated into the medical encounter than details of biomedical treatment use are into discussions with alternative practitioners. Patients' disclosure is often cautiously modulated, even by those who would welcome open communication with their physicians. When asked for their reasons for not disclosing complementary and alternative medicine use, patients indicated that they anticipated disinterest, a negative response, or an unwillingness or inability to contribute useful information from their physician. They also perceived that the complementary and alternative medicine therapies used were irrelevant to the biomedical treatment course; and that they had made choices regarding the appropriate coordination of disparate healing strategies.

In discussing health practices with patients (and, in pediatric cases, with families) it is particularly important not to make assumptions about who uses complementary and alternative medicine on the basis of stereotypes regarding age, socioeconomic status, or ethnicity. All patients have the potential to be interested in and use a variety of alternative treatments. Inquiries about complementary and alternative medicine should be a routine part of initial patient history-taking as well as subsequent visits. When the subject of complementary and alternative medicine is introduced in a respectful manner, most patients are willing to discuss it openly. Discussion should not be confined to a single interaction but part of a series of periodic inquiries to assess changes in patient interest and use of complementary and alternative medicine over time. Most patients greatly value their physicians' respect and understanding regarding treatment choices, even in the absence of mutual agreement. Patients and their families typically do not expect their physician's belief in or endorsement of particular complementary and alternative medicine therapies, but they do appreciate doctors who are respectful, willing to listen, and honest about the limitations of their own knowledge of complementary and alternative medicine.

With more information available on complementary and alternative medicine therapies and greater access to these modalities in the United States, it seems likely that their use will continue to increase. Patient care, as well as physician-patient and physician-family relationships, will benefit when comprehensive discussions of complementary and alternative medicine use are better integrated into the pediatric medical encounter.

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Prevention of adverse events in hospitalized patients using an antimicrobial review program

ABSTRACT ● **Objective** To evaluate whether an antimicrobial review system is associated with a reduction in antimicrobial-associated adverse events. ● **Design** All antimicrobial medication orders for patients hospitalized over a two-year period were evaluated. High-level interventions intended to prevent adverse antimicrobial events were collated. Based on literature estimates of adverse antimicrobial events, potential reduction of high-level adverse antimicrobial events was estimated. ● **Setting** Department of Clinical Pharmacy and Division of Infectious Diseases at a tertiary care teaching hospital. ● **Results** A total of 452 interventions were classified as "high-level." The incidence of preventable adverse antimicrobial events requiring intervention was 16 per 1000 antimicrobial orders. The incidence of high-level errors necessitating intervention was 4.4 per 1000 antimicrobial orders. An estimated 125 to 198 high-level adverse events were avoided. ● **Conclusion** An antimicrobial review program has the potential to reduce significant adverse events in hospitalized patients.

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Antimicrobial review systems are intended to optimize the safe, efficacious use of antibiotics.[1-7] Although a reduction in drug acquisition expenditures often has been realized, additional impacts on patient care have not been characterized.[1,3-5] Ideally, randomized prospective trials should be performed to document the impact of antimicrobial monitoring systems on patient outcomes. These trials are difficult to perform, however, particularly in the current healthcare environment. Using a computer-assisted decision support system, Pestotnik et al.[1] observed reduced antimicrobial expenditures and antibiotic-associated complications. While this latter investigation provides evidence for the value of the system, additional studies are necessary. The objective of the present study was to evaluate the impact of an antimicrobial review system on the reduction of adverse antimicrobial events in hospitalized patients.

Methods

The medical center at UC San Francisco uses a monitoring program through which all antimicrobial orders are reviewed.[6] When antimicrobials are prescribed, an order sheet containing patient-specific information is used. Predefined criteria, including antimicrobial dosing guidelines,[7] guide therapy. All pharmacists are certified to be competent in reviewing orders, thanks to an interactive computer-assisted training program. Staff pharmacists use a Digimedics pharmacy computer system (version 2.4; Digimedics, Scotts Valley, California) to screen all orders and determine compliance with hospital standards. With this program, significant allergies, drug interactions, and doses outside the recommended range are evaluated for all orders. General and microbiology laboratory data are accessible directly via computer. When alterations to therapy are considered necessary, recommendations are made to the prescriber. Pharmacists trained in infectious diseases, in consultation with infectious disease physicians, are available via beeper 24 hours a day.

Over a two-year study period (1 May 1994 to 30 April 1996), all high-level interventions intended to prevent adverse antimicrobial events were collated. High-level interventions were defined as (1) avoided administration of a prescribed medication to which the patient was documented to be allergic; (2) changed from low to high therapeutic index agents in patients at risk (for example, aminoglycosides in patients more than 60 years old, renal transplant); and (3) reduced dosage of low therapeutic index agents when prescribed at more than 50% above the recommended dose. All interventions were checked by a team of three reviewers to document the accuracy of categorization. Any discrepancies (10% of orders) were decided by consensus.

Models were constructed to evaluate antimicrobial adverse events, comparing the likelihood of adverse events with intervention and such a likelihood without intervention. MEDLINE literature searches were performed to estimate the incidence of a given adverse event, including known risk factors, if available.[8-32] Figure 1 provides an example of the model used to estimate the incidence of high-level interventions intended to reduce antimicrobial toxicity or adverse effects.

Results

In a total of 102,200 antimicrobial orders, 1663 interventions intended to avoid adverse antimicrobial effects took place, a rate of 16 interventions per 1000 orders.

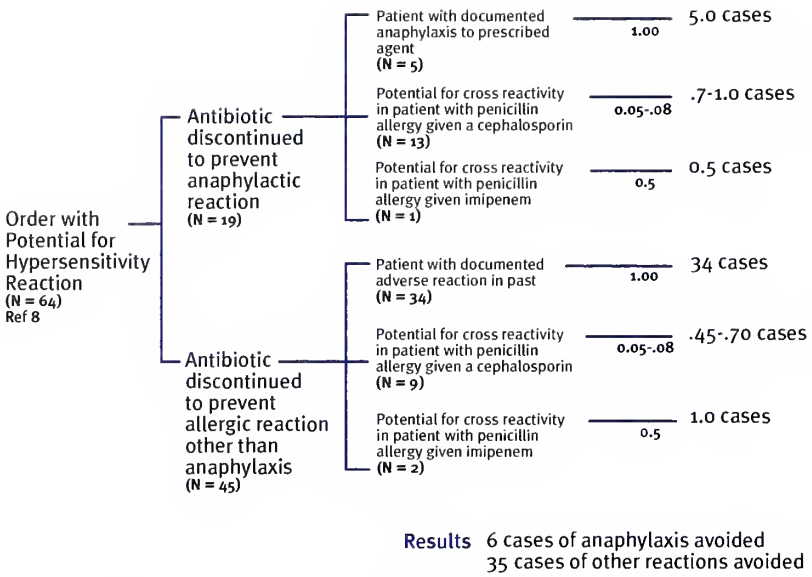

Figure 1 *Estimated avoidance of hypersensitivity reactions as a result of antimicrobial intervention*

Of these interventions, 452 were classified as high-level, 390 as moderate-level, and 821 as low-level, resulting in a rate of 4.4, 3.8, and 8.0 interventions per 1000 antimicrobial orders, respectively. Ninety percent of recommendations were accepted by the primary teams.

Table 1 documents drug-specific high-level interventions. In 64 cases (Figure 1), orders were written with potential for hypersensitivity reactions in hospitalized patients. In 19 of these cases, patients had unequivocal histories documenting an anaphylactic reaction to penicillin. In 5 of these 19 cases, penicillin was ordered by the prescribing physician but was not administered because of the intervention. Assuming a 100% likelihood of accelerated reaction in a patient with a documented history of penicillin anaphylaxis, the study strongly suggests that the intervention prevented anaphylaxis in at least five patients. In those instances in which a cephalosporin was prescribed to a patient with a documented anaphylactic reaction to penicillin (n = 13), the literature[8] suggests cross-reactivity of 5% to 8%. Thus one additional case of anaphylaxis was estimated to be avoided (13 cases × incidence of 0.05-0.08 = 0.65-1.04 cases avoided). In 45 other cases, patients with histories of allergic reaction other than anaphylaxis to the prescribed agent avoided subsequent exposure as a result of the intervention.

Prescriptions for aminoglycosides necessitated numerous interventions to reduce the dose or switch to less toxic antimicrobial therapy (cephalosporin or quinolone, for example) in patients at risk. In 127 instances, patients at risk received a dosage reduction by more than 50% or a change to alternative nontoxic therapy. Bone marrow suppression was estimated to be avoided in 7 to 25 patients receiving ganciclovir or trimethoprim-sulfamethoxazole. Penicillin or imipenem-associated seizures were estimated to be avoided in 2 to 10 patients. Other untoward reactions, including drug-induced hepatotoxicity and antimicrobial-anticoagulant interactions, were avoided, resulting in an estimated 5 to 6 less adverse antimicrobial events. As a result, a total of 125 to 198 adverse drug events were estimated to be avoided, representing 27% to 44% high-level interventions.

Discussion

It is difficult to assess the impact of an antimicrobial monitoring program. Prospective controlled trials would optimally document benefits, but these studies are difficult to perform. Retrospective or concurrent case controls raise numerous methodological problems in study design. Thus, in the current healthcare environment, the most appropriate research methodology is debatable.

We documented all interventions intended to minimize adverse antimicrobial events. Using published estimates of adverse antimicrobial events, we calculated the number of patients whose health outcomes were changed as a direct result of the interventions. Our methodology may be limited in that the estimated probability of adverse antimicrobial effect in a given patient population was based on published data. The incidence in high-risk subgroups (the elderly, for example) is difficult to document, even with agents as widely utilized as the aminoglycosides.

A second methodological problem is that while it is assumed that a regimen would continue as initially prescribed, some percentage of orders would certainly have been revised over time without the intervention. Sensitivity analysis can potentially estimate the likelihood that prescribers would change to a more appropriate order over time, but no published data are available to estimate the probability and timing of physician correction of an order with potential to cause an adverse event. In certain cases (prescribing penicillin to a patient with a documented anaphylactic reaction to penicillin, for example) sensitivity analysis would not be useful, as it would be unlikely that clinicians would be able to correct the error prior to administration. Thus, of the 41 allergic reactions among the 125 to 198 adverse events, it can be assumed that none would have been avoidable. Assuming physicians would have corrected from 0% to 100% of high-level antimicrobial orders, the intervention resulted in the avoidance of as few as 41 and as many as 198 adverse events.

Lesar et al.[33] reviewed the type and frequency of factors associated with medication-prescribing errors, observing 3.99 errors per 1000 medication orders, with errors including overdose, underdose, and other variations. Antimicrobials were associated with almost 40% of all errors. A rate of 13.55 medication errors per 1000

Table 1 *Estimated reduction in toxicity associated with antimicrobial interventions*

Toxicity	Agent	# of interventions	Published incidence of toxicity	# of cases avoided	Reference
Hypersensitivity	Various	64	5-100%	41 (Figure 1)	8
Nephrotoxicity	Aminoglycosides	127	5-50%	38-61	9-16
	Amphotericin	15	80%	12	17
	Foscarnet	6	50%	3	18
Ototoxicity	Aminoglycosides	127	2-30%	13-36	9-16
	Erythromycin	21	21%	4	19
Neutropenia	Ganciclovir	25	16-55%	4-14	20-23
	TMP/SMX	23	5-19%	1-4	24-29
Thrombocytopenia	Ganciclovir	25	4-19%	1-5	20,23
	TMP/SMX	23	2-10%	1-2	24-29
Seizures	Imipenem, penicillins	25	7-40%	2-10	30-32
Miscellaneous*	(Misc agents)	65	Varies	5-6	Various
			Total events avoided:	125-198	

*Ocular, drug-associated hepatotoxicity, anticoagulant interactions, others

antimicrobial orders, approximately equal to our findings, was documented.

Classen et al.[34] analyzed length of stay, costs, and mortality associated with adverse drug events in hospitalized patients. Compared with matched controls, patients experiencing adverse events underwent longer hospitalization stays (7.69 vs 4.46 days) and incurred increased mean cost of hospitalization ($10,010 vs $5,355). Using linear regression analysis and controlling for confounding variables, this study calculated the increase in hospital stay and in cost attributable to adverse drug events to be 1.91 days and $2,262, respectively. In addition, an increased risk of death associated with adverse drug events was observed in this investigation.

In a similar analysis, Bates et al.[35] estimated an additional 2.2-day stay and an increased cost of $3,244 associated with an adverse drug event. However, after adjusting for covariables, Bates et al. found the estimated post-event costs attributable to an adverse drug event to be $2,595 for all events and $4,685 for those considered preventable. In the current investigation, it is estimated that adverse drug events were prevented in 125 to 198 patients. Although an economic analysis was not the scope of this investigation, these cost figures for preventable adverse drug events suggest an estimated cost avoidance in this study of $585,625 to $927,630 (125-198 cases × $4,685).

While prospective controlled clinical trials are the optimal measure of the impact of an antimicrobial monitoring system, this analysis offers a reasonable estimate of the benefit of such a program. Additional analyses are needed to further document the effect of such a program on patient outcomes.

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COMMENTARY

Pharmacoeconomic decision making: a new type of medication error

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Guglielmo and colleagues found error rates of 16 per 1000 antimicrobial orders and successfully eliminated between 125 and 198 out of 452 "high-level" adverse events. These interventions improved patient care and yielded potential savings to the institution of between $585,000 and $927,000. Another type of medication "error" has less clinical influence on the individual patient but a profound impact on the broader population served. These "errors" relate to the pharmacoeconomic choices made by clinicians.

As the term suggests, pharmacoeconomics relates to the costs of drugs and their overall impact on the economics of health care. This concept has gained substantial attention as we have observed rises in pharmaceutical spending of 15% to 17% in each of the past several years, outpacing the overall rise in healthcare costs threefold. In some California environments, the cost of medications for capitated patients now exceeds the cost of hospitalizations.

Pharmacoeconomic decision making is sometimes quite straightforward. For example, the management of uncomplicated hypertension with diuretics or beta-blockers is more cost-effective than the routine use of calcium channel blockers or ACE inhibitors. Looking at a longer time frame, some pharmacoeconomic choices are also quite easily understood. Patients with recurrent peptic symptoms should be tested and treated for *Helicobacter pylori (H pylori)*. This treatment may cost more in the short term, but the subsequent reduction in the use of antisecretory agents will more than offset those costs.

Not all pharmacoeconomic choices reduce medication costs, however. Inhaled corticosteroids are underused in the management of asthma. While programs to increase their prescription and use may raise the costs of medications to the patient and to the health insurance plan, these medications reduce hospitalizations and the overall cost of health care. Similarly, the aggressive medication management of HIV has dramatically increased medication costs but has drastically reduced the need for and length of hospitalization for AIDS-related complications—and once again, has reduced overall healthcare costs.

These examples represent the "easy" errors to avoid. Unfortunately, in many cases, the proper medication choice unavoidably raises costs for both drugs and overall treatment. The management of Parkinson's disease with dopamine agonists, for example, is costly but increases patient functioning and quality of life. Similarly,

osteoarthritis treatment with nonsteroidal anti-inflammatory agents helps the patient but consumes resources.

Yet, as in the latter example, medication "errors" are rapidly increasing. The use of the new COX2 agents has grown far beyond prescription for those patients with documented GI toxicity. When clinicians routinely prescribe these more expensive agents, they commit pharmacoeconomic errors. For an individual patient, insurance may cover the majority of these added expenditures, but for the health plan, these medication decisions represent real incremental cost increases. Inevitably those costs will be passed on to the employer and, ultimately, back to the patient.

Even these choices seem logical and straightforward when compared to another set of decisions bound to create the greatest pharmacoeconomic tension among patients, clinicians, and health plans. An increasing number of newly released drugs can break budgets.

In recent history, the management of ischemic heart disease, for example, has always been expensive. We now have the choice between aspirin, at pennies per day, and the "super aspirin" platelet inhibitors (abciximab, tirofiban, eptifibatide) for patients with acute ischemia or those undergoing angioplasty. These drugs provide real, incremental, albeit small, reductions in restenosis but at a substantial cost (more than $1000 per patient).

Similarly, the management of rheumatoid arthritis has undergone an important change. Several new therapies, various tissue necrosis factor–targeted agents, have just been or will soon be released; they cost more than $5000 per patient per year. Who should receive these medications? Only those few who have failed all prior therapies or those with multiple severe joint erosions? What will be the financial consequences if clinical trials show these drugs to have benefit as first-line therapy in a vastly larger population of patients with less destructive disease?

The authors describe a prospective approach to eliminate medication errors. Their program, like others previously reported, focused upon clinical errors. With an increasing number of widely used drugs costing more than $1000 per year (cholesterol-lowering agents and proton pump inhibitors, for example), the definition of "error" needs to be expanded. We cannot avoid the pharmacoeconomic impact of our decisions. A prospective approach analogous to that presented by the authors must be considered. We need to consider not just the clinical options for managing patients but also the pharmacoeconomic impact of those options. What effect does drug spending have on the patient? Does it raise or lower the overall cost of care for that disease? What adverse consequences to the healthcare system might these choices create?

We may not want to reduce the cost of pharmaceutical spending because of the substantial benefit that these medications create. We must be mindful, however, of the choices that we make. Understanding and improving those choices has an important impact, not only on the patient in front of us but on all patients in the broader system of care.

Netphiles

The web is an excellent medium on which to publish a database, and there are now many to choose from. A large number, however, have names that are not particularly descriptive. So the US National Library of Medicine has assembled a helpful page (**www.nlm.nih.gov/databases/databases.html**) describing a selection of online databases and linking to them. This gateway page also indicates the cost of using them, although most of them are free. Despite the logical layout of the page, it is still easy to become overwhelmed by the number of databases included.

The United States Navy has produced a content-rich site called the Virtual Naval Hospital (**www.vnh.org/Misc/Outline.html**). It is a gateway of hypertext links to substantial resources that could be useful to an isolated medic in the middle of a crisis or conflict. If you can't find what you're looking for here, another sector of the site has an even larger catalogue of resources at **www.vnh.org/Providers.html**. The collection of listings is so huge that in a time of crisis users might be overloaded with data and be unable to find the required information.

—Harry Brown, Leeds, DrHarry@dial.pipex.com

We welcome suggestions for Web sites to be included in future Netphiles

Research Digest

Women's decisions to seek help for breast symptoms occur in a complex social context

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Question

How do women decide whether and when to seek medical evaluation of self-discovered breast symptoms?

Design

Analysis of narratives generated from 16 focus groups

Setting

San Francisco, CA

Participants

Eighty women aged ≥21 years, recruited through community organizations, women's groups, churches, and senior centers

Methods

Focus groups (six groups of black women, four groups of white women, and six groups of Latina women) were held in homes and community meeting rooms. They lasted 90 to 120 minutes. Women were asked what it would be like to discover a problem in their breasts and what they would do. They were also asked to relate the experiences of women in their families or communities. Sessions were audiotaped, data were transcribed, and narratives were independently analyzed by three researchers.

Main findings

Women related 104 narratives of personal experiences with self-discovered breast symptoms as well as the narratives of friends and family. They gave vivid descriptions of the place and time of symptom discovery and understood that the passage of time without treatment added to the threat of the symptom. Some disclosed the symptoms to partners or friends, which led to prompt, self-initiated visits to a healthcare provider. Others failed to disclose the discovery until their disease was advanced. Some women had difficulty interpreting the threat of the symptom and delayed evaluation. Some refused to give the symptom importance, and some blocked it from conscious awareness. Some avoided the term cancer, referring instead to "the big C." Some thought that by avoiding the term, they could exert power over the cancer, and others thought that talking about cancer would cause women to get it.

Women generally endorsed alternative therapies, often in conjunction with traditional medical treatments. Views on the role of God and spirituality varied. Those who decided not to lose the breast through surgery were seen by some as making a "breast-conserving" choice, by others as experiencing drastic repercussions, and by still others as sparing the loss of femininity. Feelings about symptom discovery included fear of cancer, fear of treatment, and guilt at not discovering symptoms earlier. Memories of the provider visit included embarrassment during the physical examination, annoyance with the discomfort of the examination, and insensitive or rushed providers. Some women delayed or refused treatment because they feared abandonment by male partners. In some instances, male partners actually obstructed diagnosis or treatment. Poverty inhibited decisions to seek an evaluation of symptoms when financial resources were needed for other family problems.

Commentary

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This study by Facione and Giancarlo provides important insights into the psychological risk factors of women's delay in seeking evaluation of breast symptoms. Although breast cancer detection practices have been studied,[1,2] issues surrounding decision making after discovering a potentially cancerous symptom have not been well examined. The findings of this study support and expand on previous research about factors that delay patients seeking treatment.[3]

Two strengths of the study are the inclusion of three ethnocultural groups and the large number of participants. Although the authors avoided recruiting from healthcare agencies, they acknowledge that volunteers may have been motivated by particular concerns about breast cancer. Only 42% of the narratives, however, were about personal symptoms, and only 6% of participants were breast cancer survivors. Although narrative analysis legitimizes the use of second-hand narratives, it would be important to extend this work to women with breast cancer. The focus group format may have led to recruitment of women who were more social than most. Also, some of the economic issues identified in this study might not apply in countries with universal healthcare coverage. Because the study shows the power of anticipated rejection by a male partner, research is needed into male partners' views and their influence on whether women seek attention for a breast symptom. Further research suggested by these findings includes the development and testing of interventions to improve information about early detection and to provide effective support for earlier decisions for treatment.

This study provides compelling insights into the complexity of decision making about breast symptoms. It sends a message that failure to act cannot be reduced simply to "ignorance requiring (better) education."

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Patients focus on integrating diabetes into their lives, while practitioners focus on glucose control

Question

Are patient and provider perspectives on the management of type 2 diabetes similar for issues of control, goal setting, evaluation of success, and treatment strategies?

Design

Qualitative, exploratory study

Setting

Public clinics and community health centers in Texas

Participants

Fifty-one Mexican-American adults who had had diabetes for >1 year and who had no major diabetes-related impairment (mean age 52.9 years, 51% men, mean annual household income $12,500) and 35 practitioners (26 physicians, 5 physician's assistants, 2 nurse practitioners, and 2 staff nurses) who had direct responsibility for patient care (mean age 43.3 years, 71% men, 51% Hispanic).

Methods

Participants were interviewed in their homes using semi-structured questions on illness history, coping strategies, perceived barriers to care, and illness management. Practitioners were interviewed with an emphasis on treating diabetes (attitudes, difficulties, and how to deal with those difficulties). Interviews were taped, transcribed, indexed, and cross-checked. Data were categorized into goals, evaluation, and strategies for dealing with diabetes.

Main findings

The goal of the participants was to integrate control of their diabetes into daily life. This goal involved an emphasis on behavior control rather than glucose control. Practitioners' goals were twofold: to achieve control over glucose concentrations and to induce patients to control their self-care behaviors (diet, drug treatment, and exercise) using instruction and motivation.

To evaluate the success of their disease management, participants did not rely primarily on glucose concentrations but were more concerned with how well they felt and were able to maintain their normal activities. For practitioners, success was based on blood glucose concentrations (glycosylated hemoglobin or fasting glucose concentrations). They also felt that poor glucose concentrations implied poor behavioral control.

For participants, strategies of care involved "taking care of myself," which included control of diabetes and necessitated balancing diabetes with other competing life factors. Practitioners emphasized self-care behaviors and getting patients to make lifestyle changes. Patient education and nutrition counseling were their main strategies. Some practitioners felt frustrated and used threats and scenarios to scare patients.

For participants, failed treatment prompted either increased vigilance or abandonment. Their poor financial situation caused patients to fear job loss if employers knew about their disease and to worry about treatment costs. Some practitioners felt that cultural factors were more important than financial factors, and some ignored finances altogether.

Commentary

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This study provides a comprehensive comparative view of the perspectives of patients with type 2 diabetes and the ptactitioners who treat patients with diabetes. Patients were concerned with the expetiential and social aspects of living with diabetes, particularly balancing and integrating diabetes and lifestyle activities, wheteas practitioners wete pteoccupied with physiological control. These findings are consistent with Hernandez's theory of integration and with subsequent studies of type 1 and type 2 diabetes.[1]

The findings of this study provide important insights into how patients with type 2 diabetes experience and interpret some of theit daily challenges. These findings point to the need for all practitionets to review their practice expectations and delivery methods and to enhance their empathy with their patients. Some caution, however, should be exetcised in generalizing these results to dissimilar practice situations: the study patients had fairly well-controlled diabetes and were Mexican Ameticans with low incomes. Only 12% of the practitioners were nurses; therefore, the findings may be more consistent with the views of physicians than of nurses. More tesearch is needed to further explicate nurses' views of patients with type 2 diabetes.

The researchers point out an additional "blind spot" of practitioners: they tended to assume that the prescribed diabetes regimen would be effective in achieving glycemic control. The assumption that adherence leads to glycemic control is simplistic and not generally supported by evidence. Researchers recommend the formation of collaborative alliances with patients as a partial solution to this problem. Practitioners who form collaborative alliances with patients can learn from their experiences and develop a deepet understanding of the complex decisions that must be made daily within a context of many consttaints. The development of collabotative alliances, which include the patient as a co-expert, can help to address psychosocial as well as physiological concerns.[2]

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Med.Pix

Anchors away

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QUESTION: A 47-year-old man comes to the office because of a new non-pruritic, non-painful dark patch that developed under his right arm during the past four months. The patient has no other dermatologic conditions or personal or family history of skin cancer, is unmarried, and denies any HIV risk factors.

On physical exam, a pigmented area is seen posterior to the right axilla (Figures 1 and 2). Although the pigmented area has the shape of an anchor, the patient denies having any tattoos or service in the Navy.

What is the differential diagnosis for this lesion and how would you proceed with making this diagnosis?

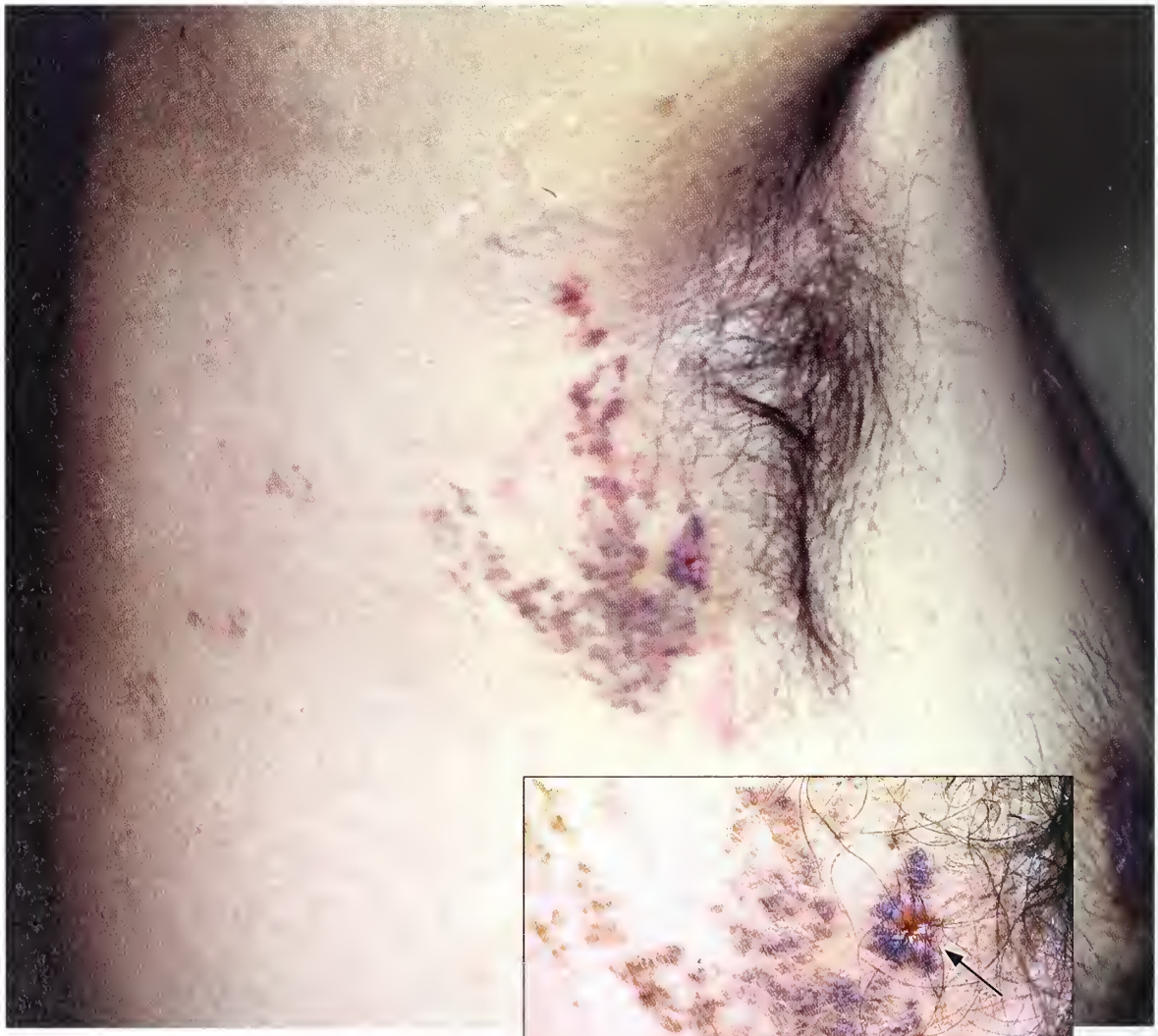

Figure 1 *Pigmented lesion. Printed with permission from Skin Surgery: A Practical Guide. Mosby-Year Book, Inc., St. Louis, 1998.*

Figure 2 *Close-up.*

ANSWER: The differential diagnosis for this lesion includes melanoma, acanthosis nigricans, lentigo maligna, solar lentigo, and postinflammatory hyperpigmentation. A full-thickness biopsy is indicated to rule out melanoma and make the diagnosis. If it turns out to be a melanoma, this full-thickness biopsy specimen is useful to measure the depth and stage of the cancer. Because the lesion is very large, a histologic diagnosis is required before considering a complete excision.

A 4-mm punch biopsy in the most suspicious area (darkest and most elevated) was performed (a small incisional biopsy would also work). The site where the 4-mm punch biopsy was performed is indicated by the arrow in Figure 2 in the lower right portion of the pigmented lesion.

The histologic diagnosis revealed melanoma Clark's level I with a total thickness of less than 0.76 mm. The remainder of the lesion was excised in the operating room and closed with sutures. The pathology report showed acanthosis with no further melanoma detected. A dermatopathologist confirmed that the original punch biopsy truly was melanoma.

Table 1 *The recommended margins for excision of confirmed and suspected melanoma. The starred numbers are based on the National Institutes of Health (NIH) consensus panel on melanoma.*

Choosing surgical margins

Melanoma	Margin during excision
Confirmed melanoma in situ (lentigo maligna)	5 mm*
Confirmed level <1 mm	10 mm*
Confirmed level 1-2 mm	20 mm
Confirmed level >2 mm	at least 20 mm
Moderate to high suspicion	1 mm
Very low suspicion	1 mm or shave

*NIH Consensus Conference. Diagnosis and treatment of early melanoma. JAMA 1992;268:1314–1319. Table adapted from Usatine R, Noy R, Tobinick E, et al. Skin surgery: A practical guide. St. Louis: Mosby-Year Book, 1998.

The patient recovered well and has remained disease-free for 10 years. Figure 3 shows the healed site with new pigment returning. Biopsy of the new pigment showed acanthosis nigricans only and no return of the melanoma.

Lessons from this case:

- Any new pigmented lesion could be a melanoma.

Figure 3 *Acanthosis nigricans developed a few months after surgery.*

- When one suspects melanoma, a full-thickness biopsy is preferred to stage the disease.
- When the lesion is large, a punch biopsy in the most suspicious area may yield the diagnosis.
- A punch biopsy or incomplete excision of a melanoma does not spread the melanoma to other parts of the body.[1,2]
- A single negative punch biopsy in a large suspicious lesion is best followed by additional punch biopsies or a larger excisional biopsy to rule out a false-negative result.

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Best Practice

CLINICAL EVIDENCE

An evidence-based review of the 10 most commonly used herbs

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Objectives

- Discuss the prevalence and use of herbal therapies in the United States
- Provide an evidence-based overview of the 10 top-selling herbs on the market
- Discuss general advice for patients who are interested in using herbal remedies
- Provide sources of information for doctors and patients

INTRODUCTION

Herbal therapies have been used throughout history but have recently undergone a renaissance. It is estimated that one in three Americans have used an herbal medication in the past year. Renewed interest in botanicals has pushed sales to an estimated $4 billion a year, with sales increasing at 20% per year since the early 1990s.[1,2]

About 25% of modern pharmaceuticals are derived from plants (see box).[2] Patients are often unaware of the similarities between medicinal herbs and prescription drugs, and they may mistakenly believe that these "natural" substances do not contain powerful bioactive ingredients. In addition, because herbs may be sold and marketed without FDA approval, there are concerns about the limited evidence on herbal side-effects, drug interactions, and product consistency. Recent reports have highlighted severe reactions to specific herbs and to contaminants in herbal preparations.[3,4] The popular use of herbs may also lead to increases in patient self-diagnosis and to delays in the use of more effective therapy. Here we review the current evidence on the safety and efficacy of the 10 top-selling herbs in the United States in 1998 (see box).[5]

Medicines derived from plants

Atropine	Belladonna and Jimsonweed
Colchicine	Autumn Crocus
Digoxin	Foxglove
Etoposide	Mayapple root
Morphine	Poppies
Quinine	Cinchona tree bark
Salicylin	Willow bark
Scopolamine	Henbane
Tamoxifen	Pacific Yew Tree
Vincristine	Periwinkle

METHODS

Articles in our review were obtained through MEDLINE (1966 to March 1999) and the Cochrane Collaboration Database of Systematic Reviews, using a keyword search of the common and Latin botanical names for each of the 10 herbs. The search was limited to English-language articles and human studies. Two authors reviewed the articles identified by the search, summarizing the evidence through a process of discussion and consensus. Statements regarding efficacy were based on the findings presented in systematic reviews and randomized controlled trials located by the search.

EVIDENCE ON THE TEN MOST COMMONLY USED HERBS

Echinacea

The species purpurea (purple coneflower) is believed to have immunostimulating effects and is most often used for the treatment or prevention of the common cold.[6] A recent systematic review identified five randomized, placebo-controlled trials of echinacea for prevention of colds and eight for treatment of colds. The authors concluded that there was insufficient evidence to make conclusions regarding the efficacy of echinacea. For a more detailed discussion of this widely used herb, see also page 198.

St. John's wort

St. John's wort is derived from the plant *Hypericum perforatum* and has been used since ancient times for depression and anxiety. It blooms around St. John's Day (June 24th) and produces a red pigment when crushed, which is believed to represent the blood of St. John the Baptist. It is the most common antidepressant used in Germany, outselling selective serotonin reuptake inhibitors (SSRIs) by fourfold. Although the mechanism of action is only partially known, it is believed to inhibit the uptake of gamma-aminobutyric acid (GABA) and other neurotransmitters.

There are several studies examining the use of St. John's wort for depression. A meta-analysis of 23 trials involving 1757 patients showed that the use of St. John's wort significantly improved scores on the Hamilton depression scale by 4.4 points (95%, confidence interval [CI] 1.78-4.01) compared with placebo. In eight of the studies, St. John's wort was also compared to low-dose tricyclic antidepressants and found to have equivalent efficacy with fewer side effects (19.8% of patients had side effects on St. John's wort compared with 52.8% on tricyclic antidepressants).[8] Currently, the National Institutes of Health is funding a $4.3 million multicenter randomized trial comparing St. John's wort to paroxetine. St. John's wort is relatively well tolerated, with only minimal side effects of gastrointestinal upset, fatigue, and phototoxicity. It is generally not recommended to be used in combination with other antidepressants.

Table 1 *A review of the evidence for the top 10 herbs*

Herb	Common uses	Dose	Side effects and interactions	Bottom line
Echinacea	Treatment and prevention of upper respiratory infections, common cold	300-400 mg dried extract tid or 2-3 mls tincture tid	Rash, pruritis, dizziness, unclear long-term effects on the immune system	Inconclusive evidence
St. John's wort	Mild to moderate depression	300mg tid of extract standardized to 0.3% hypericin	Gastrointestinal upset, photosensitivity	Beneficial in mild to moderate depression
Gingko biloba	Dementia	40 mg tid standardized to 6% terpenoids and 24% flavonoids	Mild gastrointestinal distress, headache, may have anticoagulant effects	Beneficial in patients with dementia
Garlic	Hypertension, hypercholesterolemia, atherosclerosis	600-900 mg per day, standardized to 0.6%-1.3% allicin	Gastrointestinal upset, gas, reflux, nausea, allergic reactions, and antiplatelet effects	Probable modest effect for decreasing lipids and blood pressure
Saw palmetto	Benign prostatic hyperplasia	320 mg qid or 160 mg bid	Uncommon	Probably beneficial in benign prostatic hyperplasia
Ginseng	General health promotion, sexual function, athletic ability, energy, fertility, and others	200-300 mg/day of extract standardized to > 7% ginsenosides	High doses may cause diarrhea, hypertension, insomnia, nervousness, may interact with warfarin	No conclusive evidence for any indication
Goldenseal	Upper respiratory infections, common cold	Not established	Diarrhea, hypertension, vasoconstriction	No evidence for a beneficial effect
Aloe	Topical application for dermatitis, herpes, wound healing, and psoriasis, orally for constipation	Topical doses vary, oral dose 20-30 mg hydroxyanthracene derivatives daily	May delay wound healing after topical application, diarrhea and hypokalemia with oral use	Inconclusive evidence
Siberian ginseng	Similar to ginseng	2-3 g of root daily	May alter digoxin levels	No evidence for a beneficial effect
Valerian	Insomnia, anxiety	400 mg at night	Fatigue, tremor, headache, paradoxical insomnia—not advised with other sedative-hypnotics	Inconclusive evidence

Ginkgo

Ginkgo biloba has grown in China for over 200 million years and is one of the oldest surviving tree species in the world. It is typically used to treat cognitive deficits, including Alzheimer's-type and multi-infarct dementia, and peripheral vascular disease. The active ingredients, flavonoids and terpenes (ginkgolides), are believed to act as free radical scavengers, protecting vascular walls and nerve cells as well as inhibiting platelet-activating factors, thus reducing clotting.

A large multi-center randomized placebo-controlled trial of 2020 patients with dementia found that patients using ginkgo biloba showed improvements in both Alzheimer's Disease Assessment Scale Cognitive Subscale score by 1.4 points (P=0.04) and Geriatric Evaluation by Relative's Rating Instrument score by 0.14 points (P=0.004).[9] There have also been two published meta-analyses, which concluded that gingko is effective for improving the memory and concentration of patients with cerebral insufficiency.[10,11] Ginkgo is very well tolerated but should be used with caution in patients on anticoagulants, because there have been two case reports of subarachnoid hemorrhages and hyphemas in patients using ginkgo.[12,13]

Garlic

Garlic *(Allium sativum)* has been cultivated worldwide for over 5000 years, not only to flavor food but also because it contains a sulfur-rich derivative of cysteine felt to have medicinal benefits. Historically, garlic was used in China to lower blood pressure, in Egypt to increase physical strength, and in Europe to prevent the plague. Public interest in garlic was stimulated by two meta-analyses that demonstrated a decrease in total cholesterol by 9% to 12% after treatment of at least one month.[14,15] However, eight subsequent clinical trials showed inconsistent results, with half showing no significant decrease in cholesterol and the remainder demonstrating a 6% to 13% decrease in total cholesterol.[16-23] Another meta-analysis of eight studies involving 415 patients revealed that garlic had a modest effect on blood pressure, with reductions of 7.7 mmHg in systolic blood pressure and 5.5 mmHg in diastolic blood pressure.[24] Garlic is also marketed for its antiplatelet, anti-atherosclerotic, and antitumor effects, although these indications have not been thoroughly studied. It is generally well tolerated but should probably be avoided in patients using warfarin, due to the possible antiplatelet effects.

Saw palmetto

Saw palmetto *(Serenoa repens)* is a dwarf palm tree native to the southeastern United States and the West Indies. Extract from the saw palmetto berry is widely used in Europe for the treatment of benign prostatic hyperplasia.

A-Z Photo/Bob Gibbons

Aloe Vera

In Germany, for example, 90% of patients with this condition are treated with saw palmetto or other plant extracts.[25] The mechanism of action is unknown, but several theories have been proposed, including an antiandrogenic effect, an anti-inflammatory effect through action on prostaglandins, a direct inhibition of prostate growth, or an alteration in the available sex hormone-binding globulin.[25] A recent systematic review identified 10 randomized placebo-controlled trials and concluded that saw palmetto improved urinary tract symptoms and urinary flow. When compared with patients taking placebo, patients using saw palmetto showed improvement in peak urine flow of 1.9 milliliters per second (summary of eight studies) and improvement in urine symptom scores of 1.4 points (one study, 0-19 point scale). Adverse effects due to saw palmetto were mild and comparable with placebo. The studies were limited by their short duration, variability in design, and use of different preparations.[26]

Ginseng

Ginseng, or the man-root, is the most popular and most expensive herb sold worldwide. Its scientific name, *Panax ginseng*, alludes to its purported panacea-like quality. Because the shape of the root resembles a human being, it has been believed to benefit all aspects of the human body, with presumed effects ranging from its being an immunomodulating agent to its ability to improve sexual and athletic function. As with garlic, it is difficult to substantiate ginseng's efficacy, especially given the inherent difficulty quantifying vague benefits such as "vitality" and "youthful vigor." There have been a few small poor quality studies on ginseng's effects on athletic ability, fertility, the immune system, and glucose control, but the evidence remains inconclusive.[27-30]

Adverse reactions from ginseng itself are quite rare, but there have been several case reports of side effects to contaminants in the preparations.[31] There has also been one case report of ginseng interfering with warfarin.[32]

Goldenseal

Goldenseal root *(Hydrastis canadensis)* was originally used by American Indians as an antiseptic. It is believed to have an immunostimulant effect and is currently used for upper respiratory tract infections, often in combination with echinacea. Although it accounts for 6% of all sales of herbal products in this country and approximately $240 million in out-of-pocket expenditures, there is no evidence from randomized controlled trials to support its use for this indication. High doses and prolonged use may cause diarrhea, hypertension, and vasoconstriction.

Aloe

Aloe vera *(Aloe barbadensis)* is indigenous to the Sudan and the Arabian peninsula but is now grown in many parts of the world, including the United States. Aloe may be dried into capsules or formulated into gels for topical application. Aloe is most widely used for a variety of dermatologic conditions, but studies examining efficacy are limited. One study found aloe to be beneficial for more rapid healing of genital herpes,[33] and another showed a positive result in the treatment of psoriasis.[34] Conversely, aloe was found to be ineffective for prevention of radiation-induced dermatitis,[35] and it was found to delay the healing of surgical abdominal wounds.[36] Aloe ferox, a different plant, is used in oral tablets to treat constipation, but data on effectiveness are of poor quality. Overall, the evidence for efficacy for any indication for aloe is too limited to make recommendations for clinical use.

Siberian ginseng

Siberian ginseng *(Eleutherococcus senticosus)* is not of the *panax* (true ginseng) genus, but is a popular and inexpensive substitute for ginseng. Although Siberian ginseng is touted to have the same adaptogenic and androgenic properties as true ginseng, no randomized studies substantiate its use.[37] There has been one small study on the lack of androgenicity of Siberian ginseng and a few case reports on side-effects from adulterated products.[38,39]

Valerian

The pink-flowered perennial *Valeriana officinalis* is commonly used as an anxiolytic and sleeping aid. Although initially approved in the United States to flavor foods such as root beer, valerian has over 100 constituents that are

thought to inhibit the degradation and reuptake of GABA, which may play a role in stress and anxiety. Despite valerian's popular use, there are few studies on its efficacy, safety, or interactions. Only two small randomized studies have been conducted, showing that valerian root caused decreased sleep latency and improved sleep quality without residual fatigue in the morning.[40,41] These studies were poorly done, however, and definitive conclusions cannot be drawn from them. Because it binds the same receptors as benzodiazepines and causes sedation, valerian root should not be combined with benzodiazepines, barbituates, or other sedative-hyponotics. In addition, some reports cite paradoxical stimulation, including tremor, headache, and cardiac disturbances in patients using valerian in high doses or for a prolonged period of time.

Advice for patients and doctors

Consumers should be aware that physicians are not able to guarantee the safety or consistency of products. More reliable products will likely have a label clearly stating the botanical name of the herb, milligram dose, batch or lot number, expiration date, and name and address of the manufacturer. Standardized extracts should be used whenever possible, and patients should avoid using a large variety of herbs, since herb-herb interactions are poorly described. Patients should start with the lowest effective dose and avoid using products over a long period of time, since long-term effects are generally unknown. Women who are pregnant or lactating should always avoid using herbal products unless they have been specifically tested for use in pregnancy. Moreover, all adverse effects should be reported to the Food and Drug Administration's Medwatch program (phone number 800-FDA-1088). Finally, patients and healthcare providers should educate themselves as much as possible about herbal therapeutics. Sources of information are shown in the right margin.

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Sources of information

See also page 201

Systematic reviews

The Cochrane Library. Update Software Inc. 936 La Rueda Drive, Vista, CA 92084. Web URL: http://www.updateusa.com/cochrane.htm

On-line resources

American Botanical Council http://www.herbalgram.org

Federal Drug Administration http://www.fda.gov

Phytochemical database by James A. Duke http://www.ars-grin.gov/ngrlsb/

Herb Research Foundation http://www.herbs.org

University of Washington Medicinal Herbal Garden http://www.nnlm.nlm.nih.gov/pnr/uwnhg

NIH Office of Alternative Medicine http://www.altmed.nih.org

TOPICS IN REVIEW

Herbal medicine: a practical guide to safety and quality assurance

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Herbal medicine is flourishing in the United States. Products such as St. John's wort, ginkgo, echinacea, garlic, and numerous others are advertised widely as safer, more natural, or healthier alternatives to conventional medications. Annual retail sales as of mid 1998 approached $4 billion, and, according to recent surveys, 12% to 37% of US consumers have used herbal medicines.[1,2]

Marketing of botanical preparations has changed dramatically in the last few years. Products once relegated to health food stores or vitamin and supplement chains are now widely sold in supermarkets and pharmacies. Selected insurance plans are beginning to cover herbal medicines, and large pharmaceutical companies are entering the market. Advertising sometimes mimics ads for products approved by the Food and Drug Administration (FDA), causing a situation that can be confusing for both consumers and health care practitioners.

The historical benefits of herbal medicines, and our evolving scientific evaluation of their clinical effects, are discussed in other articles in this issue of WJM. To make informed recommendations to patients about products currently on the market, however, physicians need to understand the regulatory status, safety, and quality assurance issues that affect the manufacture and sale of herbal medicines.

Summary points

- Most herbal medicines are generally safe, with only mild and infrequent side effects.
- Adverse effects can occur, and manufacturers have no regulatory responsibility to ensure safety of their products.
- Herbal products and other dietary supplements are not subject to approval by the FDA, and label claims are vague and confusing.
- There are few generic equivalents among herbal medicines in the United States. Products from different manufacturers vary considerably.
- Quality control and standardization are inherently difficult for botanical medicines, which are not regulated in the United States. Official organizations and the herbal industry are struggling to ensure quality products.

Current regulations

In 1993, the FDA proposed that those herbal medicines and other nutritional supplements not already regulated as drugs should undergo stringent marketing regulations. Intense opposition by consumer groups and the supplement industry led to a compromise decision, passed by Congress in 1994, called the Dietary Supplement Health and Education Act (DSHEA).[3] DSHEA, which classified herbal medicines (along with vitamins, minerals, amino acids, enzymes, etc.) as "dietary supplements," has created a multibillion-dollar industry. Under DSHEA, herbs can be labeled and advertised as having certain healthful or nutritional properties as long as no therapeutic claims are made. Labeling can include suggested doses, despite the fact that few dose-response studies of herbal medicines have been conducted.

Unlike pharmaceutical drugs, dietary supplements cannot be advertised for the prevention or treatment of a disease. Instead, manufacturers can describe how the supplement is intended to affect "structure and function," or the purported physiologic effect. For example, numerous European clinical studies support the use of saw palmetto to treat the symptoms of benign prostatic hypertrophy (BPH). In the United States, saw palmetto cannot be advertised as a treatment for BPH (a therapeutic claim), but it can be advertised more generally "to support healthy prostate function" or "to maintain normal urine flow." Cat's claw, an herbal medicine that lacks support by any clinical trials, is even more vaguely advertised to "help support the body's natural defenses" or "as a daily immune protectant." Nonspecific labeling statements such as these both confuse consumers and promote skepticism among healthcare professionals. Basically, manufacturers can allude to a therapeutic use of an herb, whether it is effective or not.

Herbal medicines and other dietary supplements are not subject to approval by the FDA prior to marketing.[3] Theoretically, manufacturers should be able to substantiate their "structure and function" claims, but they are not required to share this information with the FDA or make it publicly available. In fact, manufacturers are not required to notify the FDA of label claims until 30 days after their products are marketed. New dietary supplement labeling regulations, implemented in March 1999, ensure that labels include complete ingredient listings in a format that is easy to understand, but manufacturers are not required to furnish information such as side effects, contraindications, or warnings.

In European countries, herbal medicines are more strictly regulated. In Germany, where much of the Western world's scientific botanical research is done, herbal medicines are regulated and available as over-the-counter and prescription drugs. The German equivalent of the FDA requires absolute safety and has high standards for quality control. Because good clinical studies were generally not available until recently, however, approvals for herbal drugs were based on "reasonable certainty" of efficacy. Data from poorly controlled studies and traditional uses were often used to influence the approval process.[4] Many botanical medicines approved in Germany and other European countries are now widely marketed in the United States as dietary supplements.

Adverse effects

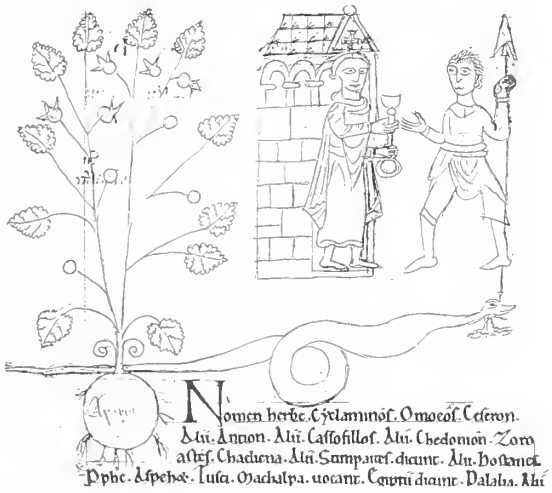
Herbal medicines owe much of their popularity to the belief that they are gentler, with fewer and milder side-effects, than pharmaceutical drugs. This is generally true. Most popular herbal medicines are relatively harmless at usual doses, with adverse effects consisting primarily of mild and infrequent gastrointestinal or dermatological reactions. Many commonly used botanicals in the United States have been prescreened for serious safety concerns by decades of use in European countries. Monitoring thousands of people who used ginkgo, St. John's wort, and kava in Europe has shown that mild side effects occur in fewer than 3% of patients.[5] Controlled studies of other popular European herbal medicines, such as echinacea, horse chestnut, saw palmetto, and valerian, have shown infrequent and mild side effects, usually similar to those seen in the placebo groups.[6-10]

In the United States, herbal manufacturers have virtually no regulatory responsibility to ensure the safety of their products. Manufacturers are not required to perform premarketing testing for safety or efficacy, and there are no mandatory requirements for post-marketing surveillance of dietary supplements. DSHEA shifted the burden of proof from the manufacturer, who previously had to prove a product safe if challenged, to the FDA, which now has the legal obligation to prove that a product is unsafe.

Although serious or even fatal consequences of herbal medicines are rare, this lack of regulatory accountability is best illustrated by the inappropriate promotion of ephedra, also known as ma huang, a traditional Chinese medicine that contains ephedrine and related alkaloids. Ephedra has been misused as a component of "natural" herbal weight loss and recreational stimulant products in the United States. Numerous reports have suggested its association with deaths, strokes, myocardial infarction, seizures, and other serious outcomes.[11] Other "medicinal" herbs and herbal preparations, such as chaparral, comfrey, germander, pennyroyal oil, and pokeweed, have significant toxicities. Their ingestion has in some cases resulted in death.[12,13] Herbal companies are marketing these herbs less often because their toxic effects are more widely recognized, but withdrawal from the market has been voluntary.

There are occasional reports in the US literature of serious adverse effects from popular herbal medicines previously thought to be harmless. For example, ginkgo biloba has been associated with intracranial bleeding in three patients; St. John's wort has been reported to cause phototoxic reactions, as well as a painful subacute neuropathy in one patient; and kava has caused extrapyramidal-like dystonic reactions in several patients.[14] Although cause-and-effect relationships are not always clear, these cases are reminders that even generally benign herbal medicines have the potential for significant adverse effects.

Serious side effects from herbal medicines are still relatively rare, especially compared with pharmaceutical drugs.



Adverse effects of appropriately prescribed pharmaceutical drugs were recently estimated to cause 106,000 deaths per year in hospitalized patients.[15] The relative scarcity of serious side effects from herbal medicines most likely reflects a combination of factors, including weaker pharmacologic activity, less consistent use, and a poorly established mechanism for recognizing and reporting adverse outcomes.

Dietary supplements currently lack sufficient regulatory controls to ensure the safety of products on the market. Time and clinical studies have found most herbal medicines to be generally safe, but botanical preparations that have pharmacologic activity have the potential for toxicity.

Quality assurance

As herbs are increasingly packaged and advertised to compete with pharmaceutical drugs, consumers and healthcare providers expect botanical products to meet comparable quality standards. Quality control and manufacturing standardization are not required of herbal medicines in the United States, however. Because botanical medicinals are classified as dietary supplements, they must comply only with the Good Manufacturing Practice (GMP) regulations for foods. The FDA is considering more extensive GMP regulations for dietary supplements, but has not yet finalized those standards.

Unlike pure pharmaceutical preparations, herbal medicinal products have few generic equivalents. Products from different manufacturers vary considerably, since it is inherently difficult to control all the factors that affect a plant's chemical composition. Environmental conditions, such as sunlight and rainfall, as well as manufacturing processes, such as selecting, drying, purifying, extracting, and storing herbs, can create substantial variability in product quality and in the concentration of plant chemicals within different products. An analogy can be made with the wine industry, which also manufactures a botanical product. Wines from the same species of grape vary substantially from different wineries, and even year to year from the same vineyard.

Choosing an herbal product: limitations and recommendations

- **Uniformity and guarantee of content quality and quantity are limited in crude natural substances or dietary supplements, therefore,**
  (1) even herbs that are well established to be effective cannot always be considered therapeutically reliable.
  (2) products from different manufacturers may vary considerably.
  (3) there is a small but real risk of contamination with an unwanted substance.
- **When possible, choose**
  (1) formulations demonstrated to be effective in well-designed clinical trials.
  (2) brands that are more likely to meet quality-assurance standards. (In the absence of specific knowledge about a manufacturer, consider products that are "standardized," marketed by major pharmaceutical firms, or contain an "NF" designation or other marker for quality assurance.)
  (3) products with detailed information on the label, including batch number, manufacturer contact information, and expiration date.

This problem is not just hypothetical. In one analysis, the concentration of constituent of St. John's wort thought to be an active ingredient varied sevenfold among different products.[16] In another study, an active chemical in different brands of garlic pills varied more than 40-fold.[17] The concentration of important constituents among 10 different ginseng products varied 10-fold in an analysis commissioned by Consumer Reports, and other analyses of ginseng products found preparations that contained no ginseng at all.[18,19] Contrast these products to standard aspirin tablets, which are mandated by law and certified to contain 95% to 105% of labeled amounts of acetylsalicylic acid and which must undergo a series of purification tests.

Concern over lack of manufacturing standards and quality control is illustrated by several recent reports of contaminated herbal products causing serious adverse effects, such as digitalis toxicity and lead poisoning.[20,21] When original reports of a variety of herbal medicine poisonings were carefully investigated, many cases were found to be due to substitution or contamination of the declared ingredients.[22] Contamination with environmental pollutants (such as microorganisms, pesticides, and toxic metals), deliberate adulteration (with nonsteroidal anti-inflammatory drugs or benzodiazepines, found in Asian patent medicines), and misidentification or mislabeling of herbal products have all been described.[22-24] Such cases are probably vastly underreported, since only serious adverse outcomes are likely to be investigated.

Standardization of specific active constituents within herbal medicines is also proving to be difficult and complex, unlike that of drug products with a single chemical entity. Standardization often implies that the preparation contains a designated percentage of a certain chemical component thought to be therapeutically active. Botanicals may contain hundreds of bioactive chemicals, however, and the compounds responsible for therapeutic activity are usually not known. Moreover, additive or synergistic activity of several constituents may be required for effectiveness. In the case of herbals, therefore, standardization is not a reliable control for pharmacologic activity; instead, it is best thought of as a control for accurate plant identification or for batch-to-batch replicability.

The United States Pharmacopeia (USP), the official organization that sets drug and other health-product standards, is establishing analytical standards for certain botanical products. Manufacturers who meet these standards can place an official "NF" (for National Formulary) on their labels. Other scientific organizations have documented analytic methods for certain botanicals, and the herbal medicine industry itself is working hard to create standardized analytic methods that can be used to self-regulate the industry. (For example, the Institute for Nutraceutical Advancement is developing a Methods Validation Program.) Trade groups have also developed their own GMP criteria in the absence of official FDA standards. Adhering to any of these quality assurance standards, however, is voluntary for US manufacturers, unlike their European counterparts.

Recommendations

This discussion of the many problems associated with regulating and assuring quality in the manufacture of herbal medicines is not meant to refute their potential benefits. Consumers and healthcare practitioners must evaluate the individual evidence for each herb's beneficial claims or effects. But after a patient decides to use an herbal preparation, especially when faced with the multitude of different products on the market, choosing a specific formulation or brand can be daunting. In the absence of any clear-cut evaluation criteria, consider the recommendations summarized on this page (see box).

If controlled clinical trials have been conducted to show an herb's effectiveness, choose the formulation used in those trials. For example, EGb761, the ginkgo extract used in a major US study and in most of the European clinical trials, is imported into the United States and sold by at least three different companies (see Table 1). Many of these products are formulated in Europe and may be more expensive, but they are presumably the most reliable for their efficacy as well as their safety. Unfortunately, however, such information is not easy to find, and some European products that have been tested do not have US counterparts.

In the absence of clinical trials, other criteria can help guarantee that products meet at least basic quality standards. Consider products manufactured or distributed by large pharmaceutical firms (for example, Warner-Lambert's Quanterra line, Boehringer Ingelheim's Pharmaton division, and Centrum Herbals by American Home Products/Whitehall-Robbins). These companies have experience with and can ensure a high level of quality control.

Warner-Lambert and Pharmaton's formulations have also been tested in clinical trials (usually in European stud-

Table 1 *Selected formulations used in European controlled clinical trials**

Herb	Use/dose	U.S. product (importer)	European product (manufacturer)
Black cohosh [25,26] *Cimicifuga racemosa*	Menopause 40 mg bid	Remifemin (Enzymatic Therapy)	Remifemin (Schaper & Brummer)
Ginkgo [27,28] *Ginkgo biloba*	Dementia 120-240 mg/day	Ginkgold (Nature's Way) Ginkoba (Pharmaton) Quanterra (Warner-Lambert) Ginkai (Lichtwer)	Tebonin [EGb761] (Schwabe) Tebonin [EGb761] (Schwabe) Tebonin [EGb761] (Schwabe) Kaveri [LI-1370] (Lichtwer)
Horse chestnut [6,8] *Aesculus hippocostanum*	Chronic venous insufficiency 250 mg bid†	Venostat (Pharmaton)	Venostasin (Klinge Pharma)
Saw palmetto [9,29] *Serenoa repens*	Benign prostatic hyperplasia 160 mg bid	ProstActive (Nature's Way) Quanterra (Warner-Lambert) ‡	Prostagutt (Schwabe) Prostagutt (Schwabe) Permixon (Pierre Fabre)
St. John's wort [6,30]§ *Hypericum perforatum*	Depression 900 mg/day	Kira (Lichtwer Pharma) Quanterra (Warner-Lambert) Movana (Pharmaton) Perika (Nature's Way)	Jarsin [LI-160] (Lichtwer Pharma) LI-160WS (Lichtwer-Schwabe) Neuroplant (Schwabe) Neuroplant (Schwabe)

Adapted from: Blumenthal M. Best prescribed herbs. HerbalGram 2000;48 (In press). Graciously supplied by Mark Blumenthal, Executive Director, American Botanical Council.
*Not inclusive of all products. See references for details of controlled trials.
†Horse chestnut seed extract is standardized to aescin. One tablet (250 mg extract) = 50 mg aescin.
‡Most European controlled studies of saw palmetto used the Permixon product (marketing is expected in the United States).
§Most European controlled studies of St. John's wort used 900 mg/day (300 mg tid). Newer studies are investigating 1800 mg/day. The Jarsin product [LI-160] and LI-160WS are slightly different formulations, but purportedly phyto-equivalent. Movana and Perika are standardized to hyperforin, a newly recognized active constituent.

ies), which gives these products a double advantage. Alternatively, choose a "standardized" product, a brand that carries an "NF" designation, or a product with a certified trade group guarantee for Good Manufacturing Practices (GMP). In addition, choose products with detailed information on the label, including batch number, manufacturer contact information, and expiration date.

Although many ethical herbal medicine manufacturers are thought to be producing high-quality products with careful identification procedures, batch-to-batch standardization, and assays for impurities, it is difficult to identify which brands and products meet even basic quality standards. In the absence of generic equivalents and regulatory standards of quality, consumers and healthcare professionals must research companies and their products individually.

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Acupuncture: its use in medicine

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A story is told in China about a peasant who had worked as a maintenance man in a newly established Western missionary hospital. When he retired to his remote home village, he took with him some hypodermic needles and lots of antibiotics. He put up a shingle, and whenever someone came to him with a fever, he injected the patient with the wonder drugs. A remarkable percentage of these people got well, despite the fact that this practitioner of Western medicine knew next to nothing about what he was doing. In the West today, much of what passes for Chinese medicine is not very different from the so-called Western medicine practiced by this Chinese peasant. Out of a complex medical system, only the bare essentials of acupuncture technique have reached the West. Patients often get well from such treatment because acupuncture, like Western antibiotics, is strong medicine. But the theoretical depth and full clinical potential of Chinese medicine remain virtually unknown.[1]

The history

Acupuncture has recently become the subject of scientific investigation, most notably as a treatment of pain, nausea and vomiting, neurologic rehabilitation, asthma, and addiction. It encompasses a range of techniques, most of which involve penetration of the skin by fine needles at defined acupuncture points. Stimulation of these areas is also accomplished and augmented by hot herbs (moxibustion), pressure (acupressure), heat, and lasers. The therapeutic modalities and traditions considered to fall under the rubric of acupuncture include acupressure, laser acupuncture, auriculotherapy, Korean hand acupuncture, moxibustion, electroacupuncture, French energetics, and myofascially based acupuncture.

Whereas acupuncture has been practiced in Asia for at least 2500 years, it did not catch America's attention until 28 years ago. James Reston, a New York Times reporter, was in China covering President Nixon's trip when he developed acute appendicitis. He brought back poignant descriptions of how acupuncture therapy helped relieve his postoperative pain.[2] The intervening years have seen an exponential growth in the practice of acupuncture in the West, as is reflected by the number of articles appearing in the popular press (Figure 1). In the 1990s, acupuncture is a complementary form of medicine used by more than a million people each year in the United States. In 1993 the Food and Drug Administration (FDA) estimated that Americans spent up to $500 million for their nine million to 12 million treatments per year.[3]

Commensurate with its upsurge in popularity, acupuncture has attracted mainstream medical attention. The FDA removed acupuncture needles from the category of "experimental medical devices" and now regulates them as common medical tools, such as scalpels and syringes, under good manufacturing practices and single-use standards of sterility.[4] In a survey of almost 4000 physicians from the United States and eight other nations practicing predominantly Western medicine, Astin found that 43% of physicians said they had referred at least one patient to an acupuncturist, and more than half believed in its efficacy.[5] The National Institutes of Health (NIH) estimated that 70% to 80% of insurers in 1996 covered some acupuncture under their policies. The following year the NIH sponsored a Consensus Development Conference on Acupuncture where clinical trials were reviewed and evidence for mechanisms of action was addressed.[6]

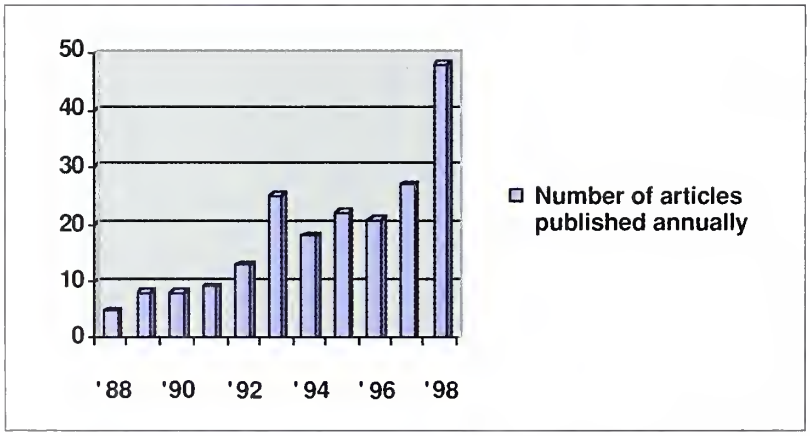

Figure 1 *Number of acupuncture articles published annually in the US popular press in the last decade. From Magazine and Journals Database of over 1000 journals and magazines, 1988 to present.*

Acupuncture according to Eastern medicine

The Yellow Emperor's Classic of Internal Medicine, Huang Ti Nei Ching,[7] written about 2300 years ago, represents the first known documentation of Chinese medicine, although it is known to have existed even before that time and to have developed over a long period. In his overview of medical acupuncture, Helms describes the essence of classical Chinese medicine. He writes:

> 'The language in classical Chinese medicine texts reflects nature and agrarian village metaphors and describes a philosophy of man functioning harmoniously within an orderly universe. The models of health, disease, and treatment are presented in terms of patients' harmony or disharmony within this larger order, and involve their responses to external extremes of wind, heat, damp, dryness, and cold, as well as to internal extremes of anger, excitement, worry, sadness, and fear. Illnesses likewise are

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described and defined poetically, by divisions of the yin and yang polar opposites (interior or exterior, cold or hot, deficient or excessive), by descriptors attached to elemental qualities (wood, fire, earth, metal, and water), and by the functional influences traditionally associated with each of the internal organs.'[8]

Qi (pronounced "chee") is the energy that flows through the body in predictable patterns, along meridians. It is determined in part by the balancing forces of yin and yang. Disruption of this flow is thought to cause disease; manipulation of the flow of *qi* with acupuncture reestablishes the balance of yin and yang and, therefore, a healthy state. Acupuncture is fundamentally different from allopathic medicine in that organs are considered energetic, not anatomic, concepts. Both diagnosis and treatment are based on measuring and adjusting the flow of energy.

Acupuncture according to Western medicine

These theories and approaches are difficult to reconcile with Western biomedical concepts of anatomy and physiology. There are no known circulatory or neuroanatomic correlates to meridians. The neural mechanism of acupuncture analgesia has been partially explained, however, through animal experiments over the past twenty years which implicate sensory nerves and endorphin release.[9] Acupuncture analgesia is initiated by stimulation of sensory nerves in muscle. These stimuli activate three centers (spinal cord, midbrain, and pituitary) to release neurochemicals (endorphins, serotonin, and norepinephrine) that block pain messages (Figure 2). The most powerful evidence for the essential role of endorphins comes from experiments showing that the opioid antagonist naloxone blocks acupuncture analgesia. Procaine infiltration of acupuncture points also blocks acupuncture analgesia, showing that afferent transmission via sensory nerves is also essential for effect.

In addition to endorphin release, acupuncture triggers the release of adrenocorticotropin hormone (ACTH) from the pituitary. ACTH stimulates the adrenal to produce cortisol. Since cortisol is known to have anti-inflammatory properties, acupuncture's efficacy in treating inflammatory conditions may also be explained by this mechanism.

Adverse reactions from acupuncture

Adverse reactions are rare, but acupuncture is not without risk. During the period encompassed by Ernst and White's review, 1969-1996, 56 articles reporting adverse effects of acupuncture were published.[10] The most common deleterious effects were infection and trauma. A total of 126 cases of hepatitis transmitted by acupuncture needles was reported. One practitioner was noted to have infected 36 patients by reusing needles. In addition, in an epidemiologic study in Japan, of 262 carriers of hepatitis C, acupuncture was identified as the likely route of infection in 20% of cases. Three case reports of HIV were found, as were individual case reports of subacute bacterial endocarditis and *Staphylococcus* sepsis.

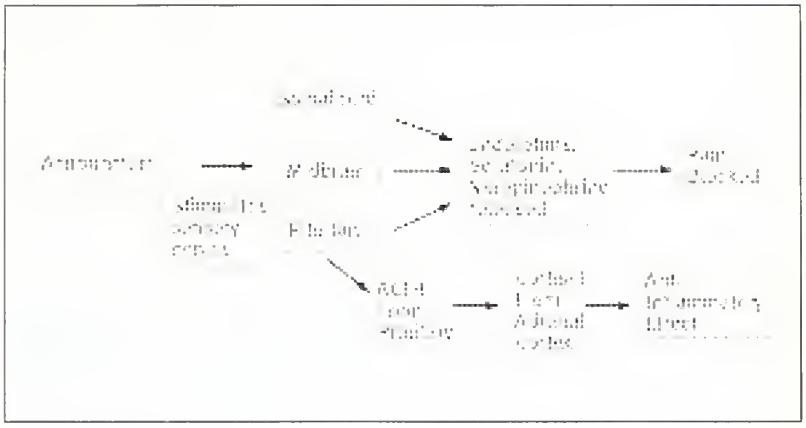

Figure 2 *Acupuncture according to Western medicine. Adapted from Pomeranz, 1996.*

Trauma is the second most prevalent adverse event resulting from acupuncture. Sixty-five case reports of pneumothorax and several reports of cardiac tamponade are noted, one occurring as a result of needle placement through a foramen in the sternum. There is also one case of pacemaker suppression by electroacupuncture. Another report implicated acupuncture in the death of a patient from asthma; in that case, in the pursuit of acupuncture treatment, conventional therapy was delayed. In a separate report, nine cases of spinal injury have been noted as well.[11] During the period studied, a total of five deaths were reported. These case reports highlight the paramount importance of the regulation of acupuncture, with particular attention paid to sterility, universal precautions, and appropriate referral for medical consultation.

Why this review

Of the million or so people in the United States undergoing acupuncture treatment, up to 70% seek this care without the knowledge of their primary care physician.[12] Eisenberg et al. suggest that this failure of communication may be due to physicians' lack of information about nonallopathic treatment modalities.[12] In this review, a summary of the research in the field of acupuncture is presented, including a discussion of the shortcomings of much of the research.

The data in context

The 1997 NIH Office of Alternative Medicine Consensus panel reviewed the scientific acupuncture litera-

ture and concluded that acupuncture is effective treatment for postoperative and chemotherapy-induced nausea and vomiting, postoperative dental pain, and acupressure for the nausea of pregnancy. They also found that acupuncture may be useful either alone or in combination with other therapy for addiction, headache, dysmenorrhea, lateral epicondylitis, stroke rehabilitation, fibromyalgia, low back pain, carpal tunnel syndrome, and asthma (see box).

Conclusions of the NIH Office of Alternative Medicine regarding acupuncture

Acupuncture is effective treatment for
- Nausea and vomiting (secondary to surgery, chemotherapy, or pregnancy)
- Pain (secondary to dental procedures)

Acupuncture may be helpful either alone or as adjunctive therapy for
- Addiction
- Asthma
- Carpal tunnel syndrome
- Dysmenorrhea
- Fibromyalgia
- Headache
- Lateral epicondylitis
- Low back pain
- Stroke rehabilitation

We conducted our own review of published meta-analyses and systematic reviews of the effect of acupuncture on a variety of conditions. Several of the reviews were published after the NIH panel met. These studies are shown in Table 1. They suggest that there is evidence for a beneficial effect of acupuncture in the treatment of low back pain, headache, neck pain, and other musculoskeletal pain; acute postoperative dental pain; nausea and vomiting of pregnancy; dilation and curettage; and cancer chemotherapy. There is also evidence of efficacy in the treatment of acute stroke. It was found that many studies have considered acupuncture for asthma and addiction, but these studies have produced either negative or inconclusive results (see Table 1).

There is a notable lack of published data for many conditions for which people seek acupuncture. Even with numerous available studies to consider, the evidence is inconsistent. In the case of back pain, for example, two of the meta-analyses included in this review demonstrated overall positive results. The other two analyses determined that the trials were of insufficient quality to conclude one way or the other. Between those with inconclusive results and those finding acupuncture to be of benefit, the essential difference was to be found in study design. The two positive meta-analyses had less stringent inclusion criteria and may therefore have included studies of lower quality.

In the current era of evidence-based medicine and managed care, we believe that good care should have a scientifically demonstrated benefit. While many Western medical practices have only recently come under closer scrutiny, a similar standard of evidence-based care should be applied to approaches like acupuncture. In the broader context of low back pain management, just as spinal manipulation has been adopted as a first-line treatment,[13] so too might acupuncture be considered a reasonable option. Acupuncture compares favorably to a variety of control interventions, and it presents little danger of adverse effects.[14]

Classical versus formula acupuncture

There are many challenges in acupuncture research, the most fundamental being the definition of the intervention itself. The Western model has generally demanded that the therapeutic intervention be standardized. This issue presents a philosophical problem, bringing Eastern and Western concepts of disease and therapy head-to-head. Acupuncture in the Eastern context is a fluid art; the treatment for the same problem in two people may be very different. To adequately assess a treatment and its effects on a number of patients compared with controls, the scientific method would seem to require that the treatment be the same for all subjects. This rigid approach may drain therapeutic benefit from the art of acupuncture. The question arises as to whether a customized treatment can be tested with scientific rigor.

Most trials to date have tested protocol or formula acupuncture, in which one problem has one treatment. This simplistic approach may not be appropriate. Acupuncturists generally treat the same problem in a variety of ways, depending on the complex characteristics of the patient. This approach has come to be known as classical acupuncture. There is some evidence from pooled data comparing classical with formula acupuncture that the former approach may be more effective,[15] but there is as yet no explanation for this observed difference in efficacy. Do classical acupuncturists spend more time with their patients, honoring unique qualities in each individual, thereby making them feel truly cared for? Does classical acupuncture involve more touching of patients, and does this promote healing in some way? Or is there something about the unique approach of the classical acupuncturists that has as yet eluded scientific definition and explanation?

Placebo acupuncture

Researchers have struggled to define an adequate placebo as a control intervention for acupuncture research. Some trials compare acupuncture to drugs and others to acupuncture at points thought to be inactive for the problem. The use of sham acupuncture points has proven problematic, however, because even nonspecif-

ic needling can lead to neurohormonal responses and clinical effects.[27]

Lao et al.[28] addressed the issues of control intervention and blinding of trials in an elegant study that sets a new standard for placebo acupuncture. In a study of the efficacy of acupuncture on postoperative oral surgery pain, subjects were randomized to receive actual acupuncture or placebo acupuncture. The former was provided by an experienced and registered acupuncturist at four acupuncture points ipsilateral to the tooth extraction site. Placebo acupuncture consisted of taping empty plastic needle tubes and needles at the skin surface of each of the same points. Both groups received manipulation at the sites in ten-minute intervals. Treatment group had needles twisted, as per usual protocol, and placebo group had palpation of the surface of the skin with a blunt dental instrument. All patients' eyes were covered with gauze so they could not see the procedure. To make the placebo more credible, mock electrical stimulation of patients in both groups was performed. No electrical current was applied, but patients were told that they may or may not feel electrical current because of its very high frequency.

To validate the blinding of patients to group assignment, all patients were asked at follow-up which treatment they believed they had received. More patients guessed wrong in both groups: 6 of 11 in the acupuncture group and 5 of 8 in the control group. In general, if research subjects do not know if they were in the treatment or control group, the placebo in use was adequate and patient blinding was accomplished. This work by Lao's group represents a crucial step forward in validating acupuncture research. With an effective placebo procedure, we can begin to study with far greater scientific rigor the effectiveness of acupuncture for a variety of indications.

Acupuncture's role in Western medicine

Eisenberg discusses strategies for introducing alternative medicine into the allopathic, Western medical setting.[29] In a context where the efficacy of some treatments is still unknown, the challenge to allopathic medical professionals is how to advise patients responsibly. Key elements are the importance of maximizing patient and provider communication and satisfaction while minimizing risk, by including a discussion with the patient about expectations and preferences and by scheduling follow-up visits to help monitor for improvement and problems. Eisenberg suggests the following type of question to initiate discussions: "Patients with [chief complaint] frequently use other kinds of therapy to find relief. For example, some patients use chiropractic, massage, herb, or vitamin therapies. Have you used or thought about using any of these or other therapies for your chief symptom, or for other reasons?"

Table 1 *A summary of meta-analyses and reviews of acupuncture efficacy*

Author (year)	Type of review	Conditions treated	Overall result
Pain			
Patel et al.[15] (1989)	Meta-analysis of 14 RCTs	Headache, neck pain, low back pain, other musculoskeletal pain	Positive
Ter Riet et al.[16] (1990)	Meta-analysis of 52 clinical trials	Headache, arthritis, back pain	Inconclusive
Ernst and White[17] (1998)	Meta-analysis of 9 RCTs	Low back pain	Positive
Tulder et al.[18] (1999)	Systematic review of 11 RCTs	Low back pain	Inconclusive
Postoperative pain			
Ernst and Pittler[19] (1998)	Systematic review of 16 clinical trials	Acute postoperative dental pain	Positive
Nausea/ vomiting (N/V)			
Dundee and McMillan[20] (1991)	Review article	N/V with dilation and curettage	Positive
		Nausea of pregnancy	Positive
		Emesis of cancer chemotherapy	Positive
		Motion sickness	Negative
Paralysis			
Naesser[21] (1996)	Review article of 8 clinical trials	Acute stroke	Positive
Asthma			
Jobst[22] (1996)	Review of 16 clinical trials	Asthma, bronchoconstriction, breathlessness, bronchitis	Inconclusive
Linde et al.[23] (1999)	Meta-analysis of 7 RCTs	Chronic asthma	Inconclusive
Addiction			
Ter Reit et al.[24] (1990)	Systematic review of 22 clinical trials	Nicotine, heroin, alcohol addiction	Inconclusive
Culliton and Kiresuk[25] (1996)	Review article	Alcohol, cocaine, nicotine addiction	Inconclusive
White and Rampes[26] (1999)	Systematic review	Smoking cessation	Negative

RCT = randomized controlled trial.

Asking about unconventional therapies or comanaging a patient who is undergoing acupuncture therapy might raise concerns about liability. According to legal scholar D.M. Studdert, no case law directly answers the question of whether a provider can be sued for a bad out-

come related to the alternative therapy.[30] Case law does state that "as a general rule, a physician's mere referral of a patient to another physician, without more, does not expose the referring doctor to liability." The most prudent referral would be to a licensed practitioner who is generally known to be competent and communicates easily with allopathic medical doctors.[30]

In 1993 the FDA estimated that there were approximately 9000 acupuncturists, both licensed and unlicensed, practicing in the United States. Acupuncture may be practiced under a specific acupuncture license or as a procedure under a medical license. In 1982 the Council of Colleges of Acupuncture and Oriental Medicine (CCAOM) was formed. They have developed academic standards as well as curriculum requirements for both master's and doctoral level programs in acupuncture. As of 1996, 25 colleges were members of CCAOM, with membership open to any established 3-year acupuncture program that met the 14 requirements of the National Accreditation Commission of Schools and Colleges of Acupuncture and Oriental Medicine. The American Academy of Medical Acupuncture (AAMA) represents physician acupuncturists. Full membership requires a minimum of 220 hours of formal training and 2 years of clinical experience, as outlined by the WHO. In 1995 there were an estimated 10,000 certified acupuncturists in the United States, approximately one third of whom were medical doctors.[31]

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capsule

The pill is safe for women with Crohn's disease Oral contraceptives have little impact on the severity of Crohn's disease, French researchers have found, although many women with the disease are advised to avoid them (Gut 1999;45:218-222). In a study of over 300 women with stable disease, women who used oral contraceptives did not have any more flare ups during follow up than the rest. Smoking, on the other hand, emerged as a clear risk factor. Women with Crohn's disease should be allowed the same choice of contraceptives as everyone else, the researchers conclude.

Adverse reactions to watch for in patients using herbal remedies

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Alternative medicine has increased in popularity in the United States. In 1997, an estimated $27 billion was spent on alternative therapies; at that time, the use of herbal remedies had increased 380% compared with 1990.[1] The dietary supplement industry, which manufactures many herbal products, represents a $13 billion market with $3.24 billion in sales.[2] The passage of the Dietary Supplements Health and Educational Act (DSHEA) of 1994 allowed dietary supplement manufacturers to make certain functional claims on labels, shifting the burden of proof regarding toxicity from the seller to the regulator. Herbal remedies are considered food products under the DSHEA and hence are not subject to rigorous clinical testing, as are pharmaceutical products. No manufacturing standards regulate the quality and production of herbal remedies. All these factors have led to increased adverse reactions in patients choosing alternative therapies. It is imperative that physicians and healthcare providers inquire into their patients' use of herbal remedies and become knowledgeable about potentially adverse effects of herbs and possible drug-herb interactions.

A-Z Photos/K D Miller

St. John's Wort

Adverse reactions associated with dietary supplements, especially herbal remedies, can be caused by inherently toxic herbs, by herb overdoses, or by drug-herb interactions, especially with pharmaceuticals that have a narrow therapeutic index. They can also represent idiosyncratic reactions to herbs, such as allergic responses or anaphylaxis. Other adverse reactions can be due to adulteration caused by manufacturing and quality problems, misidentification, substitution of one herb for another, variability in the amount of active ingredients, inaccurate or incomplete label identification, improper processing and preparation, or contamination.

Table 1 lists some herbs commonly used by consumers, as well as indications, potential adverse reactions, and possible drug-herb interactions. Additional information can be obtained from recent review articles on herbs[3-5] and potential drug-herb interactions.[6-9] It is important to realize that personal experience is not a reliable basis for the exclusion of uncommon reactions to herbal remedies.[10] A patient with generally stable reactions to an herbal remedy may still experience an adverse reaction, since there may be batch-to-batch variations and/or accumulation of toxic components. Physicians who are treating patients suspected of herb-related adverse reactions are encouraged to contact the US Food and Drug Administration's MEDWATCH program or the local poison control center, so that data can be collected and analyzed.

Methods

This review article is based on a literature search using MEDLINE and other reference source material.[7,11] The MEDLINE search included the following keywords: herbs, herbal, traditional Chinese medicines, toxicity, adverse effects, death, drug interaction, and pharmacokinetic. Specific searches were performed combining these keywords with the common names and scientific names of plant products.

Adverse reactions

The most common herbs used in alternative therapies are listed in Table 1. Other commonly used herbs can cause adverse reactions as well, including the following:

Siberian ginseng *(Eleutherococcus senticosus)* has been implicated in causing hypertension in a female who had been taking the product for 15 years. Rechallenge with the same product was repeated twice, causing a rise in blood pressure.[12]

Dang gui *(Angelica sinensis)* binds to estrogen receptors and promotes uterine growth. It could potentially stimulate estrogen receptor-positive cancer cells, a risk for women with breast cancer.[13]

Advice for patients who use herbal remedies

- Treat herbal remedies as medicinal products, not food products. "More" does not mean "better."
- Do not exceed recommended dosage and do not use herbal remedies for a prolonged period of time. A good rule of thumb is no more than four weeks unless under the supervision of a healthcare provider.
- Patients with serious diseases should consult a physician before using herbal remedies.
- Herbal remedies can interact with other pharmaceutical products. Consult a physician or a pharmacist when using herbal remedies in conjunction with pharmaceuticals.
- If side effects develop, stop taking the herbal remedies and consult a physician.
- Purchase herbal remedies only from reputable sources.
- Do not use herbal remedies during pregnancy and lactation unless directed to do so by your physician.
- Do not give herbal remedies to infants or young children.

Table 1

Common name (scientific name)	Conditions treated and other uses	Side effects/ safety issues	Drug interactions, if any
Echinacea [*Echinacea pallida* (Nutt.) and *Echinacea purpurea* (L.) Moench]	Common cold URT infection[11,48,49] * § Lower UTI[11] * § Immune stimulation[50] *	Anaphylaxis[51] Contraindicated in multiple sclerosis, collagenosis, HIV infection, tuberculosis[7,11]	None known or substantiated
Feverfew (*Tanacetum parthenium*)	Arthritis[52] † Migraine[53] *	Inhibits human blood platelet aggregation[54] Contact dermatitis[55]	Warfarin or other anticoagulants May reduce effectiveness of NSAIDs by inhibition of prostaglandin[56]
Garlic (*Allium sativum* L.)	Hyperlipidemia (adjunct treatment)[11] § Familial hyperlipidemia (pediatric)[57] † Hepatopulmonary syndrome[58] * Hypercholesterolemia[59,60] † Platelet aggregation[61,62] *	GI symptoms[11] Allergic reactions including contact dermatitis, asthma, rhinitis, urticaria[63]	Caution in patients stabilized with warfarin[6] and antiplatelet drugs May increase serum insulin levels[7]
Ginger (*Zingiber officinale* Roscoe)	Dyspepsia and motion sickness[11,64] * § Nausea and vomiting (prevention)[45,65,66] * Thrombosis[67,68] * Rheumatism and musculoskeletal disorders (pain relief)[69] *	Contact dermatitis[70]	Caution in using antiplatelet drugs
Ginkgo biloba (*Ginkgo biloba* L. leaf)	Erectile dysfunction[41] * Antidepressant-induced sexual dysfunction (predominantly that caused by SSRIs)[42] * Alzheimer's disease[11,35,71] ‡ § Asthma (reduces airway inflammation)[72] * Chronic schizophrenia (additive effect with fewer side effects)[73] * Cerebrovascular ischemia[74] * Oxidative stress in cardiovascular surgery (adjuvant therapy)[75] * Intermittent claudication[11,37] * § Irradiation (anticlastogenic effect)[76] * Vertigo, dizziness, tinnitus caused by vestibular disorders[11,39,40] * § Symptoms of premenstrual syndrome[77] *	Inhibits platelet-activating factor[78] Intracerebral hemorrhage[79]	May compete for MAO inhibitor[80] May cause bleeding when combined with NSAIDs, anticoagulants, and anti-platelet drugs[81] Interaction with thiazide diuretic, causing hypertension[12]
Ginseng (*Panax ginseng* C.A. Meyer)	Fatigue, decline in capacity for work and concentration[11,82,83] * § Common cold (prevention)[86] * Cancer (prevention)[88] * Also: Enhances exercise performance[84,85] * Immunomodulatory effects[87] *	Androgen effect[89]	Interacts with warfarin and other anticoagulants[7,8] May interact with phenelzine and other MAO inhibitors[90] Not advised with stimulants, antipsychotic drugs, or hormones[7]
Goldenseal (*Hydrastis canadensis* L.)	Malaria[91] * Diarrhea[92,93] * Ventricular tachyarrhythmias[94] *	Acute hemolysis in babies with G6PD deficiency[95]	Contraindicated in neonates with jaundice and pregnant women[96] May antagonize heparin[7]
Saw palmetto (*Serenoa repens* [Bartram] Small)	Benign prostatic hypertrophy[11,34,97] ‡ §	GI symptoms[98]	Avoid with hormone therapy (e.g., estrogen and oral contraceptives)[6]
St. John's wort (*Hypericum perforatum* L.)	Mild depression/anxiety[11,36,99] ‡ § Topical myalgia, burn[11] * § Also: Wound-healing, anti-inflammatory, and analgesic activity[100] *	GI symptoms, dizziness/confusion, tiredness/sedation, photosensitivity[101,102] Inhibition of sperm motility[103]	May potentiate MAO inhibitors and SSRIs[7] May interact with drugs binding to μ-opioid receptor (e.g., known photosensitizers such as piroxicam or tetracycline)[6]
Valerian (*Valeriana officinalis* L.)	Restlessness, sleeping disorders[11,105,106] * §	Cardiac complications and delirium associated with withdrawal[107]	Prolongs sedation from barbiturates[6] Additive effects with benzodiazepine[108]

*More information needed; †probably not effective; ‡probably effective; §from German Commission E Monograph. In 1978, the German Ministry of Health established Commission E to review the safety and efficacy of phytotherapy and herbal substances; the Commission has published a total of 462 monographs[11]. G6PD: glucose-6-phosphate dehydrogenase; GI: gastrointestinal; MAO: monoamine oxidase; SSRI: selective serotonin reuptake inhibitors; NSAID: nonsteroidal anti-inflammatory drug; SSRI: selective serotonin reuptake inhibitor; URT: upper respiratory tract; UTI: urinary tract infection.

Aconite *(Aconitum carmichaeli)* poisoning is probably the most common cause of cardiac toxicity among people taking Chinese herbs. Clinical presentation typically includes numbness and paresthesia beginning in the mouth and spreading to the limbs, as well as dizziness, nausea, vomiting, weakness, sweating, and palpitations. The conscious state may be reduced. With severe poisoning, hypotensive sustained ventricular tachyarrhythmias may develop, often complicated by acidosis and hypokalemia. The poisoning is reversible with supportive therapy.[14]

Chaparral *(Larrea tridentata),*[15] **germander** *(Teucrium chamaedrys),*[16] **jin bu huan** *(Lypocodium serratum,* which contains levo-tetrahydro-palmatine),[17,18] **ephedra** species (**ma huang**),[19] and **syo-saikoto-to** (a mixture of seven herbs),[20] among other herbs, have been associated with toxic hepatitis.

Toxic hepatitis shows no specific pattern of symptoms and is difficult to diagnose. When considering herbs as a cause for toxic hepatitis, physicians will frequently rely on the elimination of other causes and a temporal relationship between ingestion of herbs and onset of hepatitis and between withdrawal of herbs and recovery. Autoimmune hepatitis triggered by an herbal formula, dai-saiko-to, has also been reported.[21] It was hypothesized that the immunostimulating effects of the formula may have modulated the latent autoimmunity of the patient.

Pyrrolizidine alkaloid—which is found in *Crotalaria assamica Benth* and *C sessiliflora* of the Leguminacae family, *Sencio chrysanthemoides* and *S scandens Buch-Ham* of the Compositae family, *Packera candidissima,*[22] and Eupatorium species—has been shown to induce hepatic veno-occlusive toxicity and can have similar effects on an unborn fetus.[23] Not all pyrrolizidine alkaloids are hepatotoxic, however, depending on the structure activity of the pyrrolizidine nucleus.[24] Symptoms of pyrrolizidine alkaloid poisoning in veno-occlusive disease include arterial hypertension and right ventricular hypertrophy,[22] abdominal pain, ascites, hepatomegaly, and raised serum transaminase levels.[25]

Licorice root (*Glycyrrhiza glabra* L.), which contains glycyrrhizin, has also been reported to be associated with Fanconi syndrome.[26] Other herbs related to renal toxicity may be secondary causes, with toxicity due instead to adulteration with pharmaceutical products (for example, mefenamic acid[27]) or contaminants.

Ephedra products have been associated with adverse events, including deaths related to myocardial infarction and cerebrovascular accident. Many products that contain ephedra also contain multiple stimulants such as caffeine and are marketed for weight loss, energy and performance enhancement, body building, and as substitutes for street drugs.[28] All the claims and ingredients connected with these products are clear deviations from the traditional Chinese medicinal usage of ephedra for asthma and pulmonary diseases.

A-Z Photo/Robert Erwin

Ginger

Chinese patent medicines, imported herbal products formulated into pills and tablets, often cause adverse reactions. They may contain natural toxins, heavy metals, or pharmaceuticals.[29] Cinnabar (mercuric sulfide), realgar (arsenic sulfide), or litharge (lead oxide) may be present as part of the traditional formula. Other common toxic herbal ingredients found in these imported patent medicines include borneol (similar to camphor), aconite, bufo secreta (toad secretion or bufotoxin), mylabris, scorpion, borax, and *Strychnos nux vomica* (strychnine).

Drug-herb interactions

Drug-herb interactions are an important consideration, especially regarding pharmaceutical products with narrow therapeutic indexes. Because herbs contain pharmacologically active compounds, potential drug interactions can occur when multiple herbs are used or when pharmaceuticals are administered to a patient using herbs.

Papaya extract, which contains papain, caused an increase in the International Normalized Ratio (INR) in a patient previously well-maintained on warfarin. After withdrawal of both warfarin and papaya extract, the patient's INR returned to normal. Papain is contraindicated with warfarin, since it may damage the mucous membranes of the gastrointestinal tract and result in increased bleeding.[12]

Ginkgo biloba and thiazide diuretic can interact to cause hypertension.[12]

Feverfew, garlic, ginkgo, ginger, and **ginseng** may alter bleeding time. When used concomitantly with warfarin, close monitoring is advised.[6]

Kava-kava (*Piper methysticum* F.) is used mainly for its euphoric effects. When combined with benzodiazepine, it may result in a semicomatose state.[7] It should not be used with barbiturates, antipsychotics, or alcohol.[8]

Licorice (*Glycyrrhiza glabra* L.) can potentiate the effect of cardiac glycoside. Close monitoring is required when the two are used concomitantly.[7]

Questions physicians should ask their patients

- Is the patient using any dietary supplements? Be specific with questions and be sure the answer includes use of vitamins, minerals, herbs or other botanicals, amino acids, concentrates, metabolites, extracts, or other dietary substances.
- If the patient is using dietary supplements, what is the dosage formulation and what are the directions for use?
- Is the patient seeing an herbalist, acupuncturist, naturopathic practitioner, or natural healer?
- What is the dietary supplement for? (Asking this question allows patients to express their knowledge as well as any untold symptoms or complaints.)
- If the herbal remedies require preparation on the part of the patient, ask for more details about the procedure and the patient's source of information about that procedure.
- Has the patient observed any serious side effects from the herbal remedies?
- Is the patient taking any other over-the-counter or prescription medications?

Communication with patients

It is important for physicians and other healthcare providers to establish open communication with their patients regarding the use of dietary supplements. Many patients are unwilling to inform their physicians, fearing disapproval and perceiving a lack of knowledge and understanding in their physicians. Inquiring about the use of herbs, vitamins, and other remedies should be part of normal history taking, along with other questions about social habits and background. Physicians often talk with patients about controversial subjects, so discussing the merits and drawbacks of herbs does not require new skills.[30] When communicating with the patient, the physician should pose questions that are direct, neutral, and nonjudgmental.[31]

Patients often consider herbal remedies as natural products or food and not as medicine. They assume, therefore, that herbal remedies are free from side effects. Physicians need to emphasize that many pharmaceuticals were originally derived from plant products and that herbal remedies can be as potent as pharmaceuticals. Physicians need to ask specific questions regarding the the use of vitamins, minerals, herbs or other botanicals, amino acids, concentrates, metabolites, extracts, and any other dietary substances being used by their patients. They should also obtain information about directions for use, methods of preparation, and dosage formulations.

It is especially important for physicians to inquire about method of preparation when raw botanicals are being used. In traditional Chinese medicine, prescriptions frequently consist of decoctions of a number of different herbs. Such an herb decoction is a concentrated extract, usually prepared by boiling the herbs in water until the mixture is reduced to a small volume. Knowing the method by which an herbal remedy has been prepared is important, because many toxic herbs can become relatively safe for use if they have been processed properly. For example, aconiti tuber toxicity can be greatly reduced after the plant material is specially prepared through heat and water extraction.[32] There are five reported cases of podophyllotoxin toxicity due to ingestion of *Dysosma pleianthum* or bajiaolian, a species of mayapple prescribed in traditional Chinese medicine. Toxicity responses ranged from nausea and vomiting to abnormal liver function tests and central nervous system disturbance. The inconsistent relationship between doses and clinical severity of symptoms might be due to different methods of preparation.[33]

Patients should be asked whether they have consulted with other healthcare providers, e.g., acupuncturists, herbalists, naturopathic practitioners, or natural healers. Asking this question directly will often reveal other complaints, other symptoms, or the choice of alternative treatments, including dietary supplements. All this information will assist physicians in making the proper diagnosis. Physicians should speak with patients about the efficacy and toxicity of herbal remedies, basing the discussion on firm knowledge and scientific fact, and about potential drug-herb interactions and side effects of herbal remedies. By the same token, patients and providers alike must acknowledge that as long as information on the efficacy and toxicity of alternative therapies remains inadequate, advice will remain imperfect and a matter of judgment rather than fact.[31]

Herbal products as treatment options

An increasing number of scientifically based clinical trials are being conducted on the efficacy of herbal remedies and comparing herbs and pharmaceuticals for the treatment of different diseases. Although some of the herbal remedies have shown promise, no large clinical trials have yet demonstrated efficacy equal to that of pharmaceuticals for clearly defined disease states.[34-36]

The following herbs show some promise in treating various diseases, especially when current treatments are inadequate.

Ginkgo biloba has shown promise in the treatment of patients suffering from peripheral occlusive arterial disease. It causes a significant and therapeutically relevant prolongation of patients' walking distance.[37] It may be effective in the treatment of patients with circulatory encephalopathy[38] and can considerably improve oculomotor and visuovestibular function in patients complaining of vertigo or dizziness caused by vascular vestibular disorders.[39,40] Ginkgo may have beneficial effects in erectile dysfunction and sexual dysfunction caused by selective serotonin reuptake inhibitors.[41,42]

Dang gui (*Angelica sinensis*) may be useful in relieving menopausal symptoms, especially in women who

have ruled out prescription drugs and are not at risk of breast cancer.[13]

Milk thistle (*Silybum marianum gaertn*) contains silymarin, which acts as liver-protective agent. This herb shows promise in treating *Amanita phalloides* mushroom poisoning[43] and a variety of liver disorders, including hepatitis.[44]

Ginger and **pyridoxine** (vitamin B_6) may be beneficial for nausea and vomiting resulting from pregnancy.[45]

Asian ginseng (*Panax ginseng* C.A. Meyer) may protect against radiation and liver toxicities.[46]

Shi-Quan-Da-Bu-Tang ("Ten Significant Tonic Decoction" or "SQT") consists of a mixture of ten medicinal herbs and may reduce the adverse effects caused by chemotherapeutic agents and radiation in cancer patients.[47]

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Probiotics and prebiotics: can regulating the activities of intestinal bacteria benefit health?

Colonic microflora are important to health. The growth and metabolism of the many individual bacterial species inhabiting the large bowel depend primarily on the substrates available to them, most of which come from the diet.[1,2] This has led to attempts to modify the structure and metabolic activities of the community through diet—using probiotics and prebiotics. Probiotics are live microbial food supplements. The best known are the lactic acid bacteria and bifidobacteria, which are widely used in yogurts and other dairy products. These organisms are nonpathogenic and nontoxigenic, retain viability during storage, and survive passage through the stomach and small bowel. Prebiotics are nondigestible food ingredients that selectively stimulate the growth, activity, or both, of lactobacilli or bifidobacteria in the colon, thereby improving health.

Bacteria and yeasts used as probiotics

Bifidobacterium longum
B breve
B infantis
B bifidum
B adolescentis
Lactococcus cremoris
L lactis
Enterococcus faecium
Lactobacillus rhamnosus
L acidophilus
L casei
L bulgaricus
L gasseri
Saccharomyces boulardii
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Competing interests JHC has been reimbursed for speaking at a conference sponsored by Ross Laboratories, which manufactures artificial feeds containing prebiotics. JHC and GTM received European Union funding for a project on nondigestible oligosaccharides in which Orafti, Belgium, which manufactures prebiotics, was a partner. JHC is a temporary consultant to Lamberts Healthcare, which sells prebiotics and probiotics.

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The probiotic concept

Since probiotics do not permanently colonize the host, they need to be ingested regularly for any health-promoting properties to persist. Most studies on probiosis have been observational rather than mechanistic, and thus the processes responsible for many probiotic phenomena are seldom explained. Some probiotics are members of the normal colonic microflora and are not viewed as being overtly pathogenic. These organisms have occasionally caused infections in people whose health is compromised in other ways, however.[3,4]

Commercial probiotic preparations are usually mixtures of lactobacilli and bifidobacteria, although yeasts such as saccharomyces have also been used (see box). Bifidobacteria are of particular interest. These are anaerobic pleomorphic rods or club-shaped organisms (Figure 1) that normally have an important role in breaking down dietary carbohydrate and interact directly with the host metabolism.[5] Bifidobacteria also synthesize and excrete water-soluble vitamins, but there are considerable differences in species and strains.[6] These organisms predominate in the colons of breast-fed babies; they account for up to 95% of all culturable bacteria and protect against infection.[7] Bifidobacteria do not occur in such high numbers in adults.

Adherence

Attachment of probiotics to the gut epithelium is an important determinant of their ability to modify host immune reactivity, but this is not a universal property of lactobacilli or bifidobacteria and is not essential for successful probiosis.[8] Adherence of *Lactobacillus acidophilus* and some bifidobacteria to human enterocyte-like CACO-2 cells prevents binding of enterotoxigenic and enteropathogenic *Escherichia coli*, as well as *Salmonella typhimurium* and *Yersinia pseudotuberculosis*.[9,10] *Bifidobacterium infantis* and some strains of *B breve* and *B longum* attach strongly, although other *B breve* and *B longum* isolates are poorly adherent. Thus there are species and strain variations in this probiotic attribute.

Nineteen strains of lactobacilli (each 5×10^6/ml) were fed to healthy volunteers in 100 ml of fermented oatmeal soup.[11] Biopsy specimens showed that the organisms colonized jejunal and rectal mucosas. Adherent lactobacilli were recovered from jejunal samples 11 days after the probiotic was stopped, while mucosal clostridia decreased up to 100-fold in some volunteers. In rectal tissue, anaerobes and enterobacteria were reduced.

Figure 1 *Gram-stained preparation of Bifidobacterium adolescentis showing club-shaped cells and other pleomorphic forms*

Probiotics and gut infection

Colonic microflora normally present a barrier to invading organisms, but pathogens often become established when

Table 1 *Chemical composition and characteristics of candidate prebiotic carbohydrates*

Oligosaccharide (example)	Chemical composition
Fructo-oligosaccharides (Raftilose P95)	95% oligosaccharides β (2-1) fructan; 60% glucose, $fructose_{(n)}$, 40% $fructose_{(n)}$ dp 2-8, average dp 4-5
Inulin	>99% oligosaccharides β (2-1) fructan; average dp 10-12
Pyrodextrins	Complex mixture of glucose-containing oligosaccharides
Transgalactosylated oligosaccharides (Oligomate 55)	Mainly 6′ galactosyllactose, dp of oligosaccharide fraction 2-5 (primarily dp 3); 55% pure
Galacto-oligosaccharides	Oligogalactose (85%), small amounts of glucose, galactose, and lactose
Soy oligosaccharides	Stachyhose (fructose, galactose, galactose, glucose) and raffinose (fructose, galactose, glucose), dp 3-4
Xylo-oligosaccharides	β (1-4) linked xylose; 70% pure, dp of oligosaccharide fraction 2-4
Isomalto-oligosaccharides	Mixture of α (1-6)-linked glucose oligomers (isomaltose, panose, isomaltotriose)
Lactulose	Galactose and fructose-containing disaccharide

dp = degree of polymerization.

the integrity of the microbiota is impaired through stress, illness, antibiotic treatment, changes in diet, or physiological alterations in the gut. Bifidobacteria are known to be involved in resisting the colonization of pathogens in the large bowel.[12] Feeding *B breve* to children with enteritis eradicated *Campylobacter jejuni* from their stools, although less rapidly than in patients treated with erythromycin.[13] Supplementation of infant formula milk with *B bifidum* and *Streptococcus thermophilus* reduced rotavirus shedding and episodes of diarrhea in children in the hospital.[14]

Lactobacilli have been widely used in treating diarrheal diseases such as pseudomembranous colitis, but the results have been mixed.[15] Feeding freeze-dried powders of *L acidophilus* NCDO 1748 had no effect on patients with pseudomembranous colitis,[16] but lactobacillus GG successfully eradicated *Clostridium difficile* in five patients with relapsing colitis.[17] Viable lactobacilli (approximately 10^{10}) were fed daily in skimmed milk. Diarrhea was immediately relieved in four patients, and there were concomitant reductions in titers of *C difficile* toxin in stools. The other patient also improved after further antibiotic and probiotic treatment. Lactobacillus GG had previously been shown to colonize the gut and secrete an antimicrobial product that was active against *C difficile* and a range of other micro-organisms.[18]

Not all lactobacilli are effective in combating enteric pathogens, however. Twenty-three healthy volunteers were given a commercial product containing *L acidophilus* and *L bulgaricus* and were then challenged with enterotoxigenic *Escherichia coli*.[19] They did not differ in respect of attack rate, incubation period, or duration of illness from control subjects given a placebo.

The yeast *Saccharomyces boulardii* has also been used in studies of the prevention and treatment of diarrhea associated with *C difficile* infection.[20] Of 180 patients in a double-blind controlled study, 9.5% of those receiving the probiotic had diarrhea compared with 22% of the controls given placebo. The authors concluded that prophylactic use of the probiotic reduced the incidence of diarrhea associated with *C difficile* infection, although *S boulardii* did not prevent acquisition of the pathogen.

Traveler's diarrhea

Lactobacilli, bifidobacteria, enterococci, and streptococci have been used prophylactically to prevent traveler's diarrhea caused by enterotoxigenic *E coli*. Neither *L acidophilus* nor *Enterococcus faecium* had any probiotic effect on groups of Austrian tourists,[21] and no differences were observed in healthy volunteers given either placebo or lactobacilli, who were then challenged experimentally with virulent enterotoxigenic *E coli*.[19] The incidence of diarrhea was reduced from 71% to 43%, however, in tourists going to Egypt who were given capsules containing *S thermophilus*, *L bulgaricus*, *L acidophilus*, and *B bifidum*.[22]

Prebiotics

To be effective, prebiotics should escape digestion in the upper gut, reach the large bowel, and be utilized selectively by a restricted group of micro-organisms that have clearly identified, health-promoting properties. The food ingredients most likely to meet these criteria at present are oligosaccharides, including inulins, and their derivatives, the fructo-oligosaccharides (see Table 1). These low-molecular-weight carbohydrates occur naturally in artichokes, onions, chicory, garlic, leeks, and, to a lesser extent, cereals. Other oligosaccharides such as raffinose and stachyose are the major carbohydrates in beans and peas. These simple molecules can also be produced industrially, and a number of new potential prebiotics are being developed for this market (see below). The degree of polymerization of these substances (Table 1) refers to the number of individual monosaccharides in the molecule.

Not all nondigestible oligosaccharides have prebiotic properties. Inulin, fructo-oligosaccharides, and to a lesser degree, galacto-oligosaccharides dominate the published reports (Table 2). Fructo-oligosaccharides have an energy value of 6 kJ/g; they have no genotoxic, carcinogenic, or toxicological effects; and they are mildly laxative, although flatulence is often a complaint when large doses are taken.[23] In controlled dietary studies with human volunteers, fructo-oligosaccharides (15 g/day) increased fecal bifidobacterial numbers tenfold while reducing clostridia and

enterobacteria counts, showing that the species composition of the microbiota could be selectively manipulated through diet. In vitro, eight different bifidobacterial species that were grown on fructo-oligosaccharides produced inhibitory substances that were antagonistic, to various degrees, against salmonella, listeria, campylobacter, shigella, and vibrio.[24] Feeding fructo-oligosaccharides (8 g/day) to elderly people increased fecal bifidobacteria tenfold,[25] and ingestion of soybean oligosaccharides (10 g/day) resulted in a smaller, though still appreciable, increase in bifidobacteria.[26] Fructo-oligosaccharides do more than promote bifidobacterial growth, however, and several other intestinal bacteria are clearly involved in their metabolism.[27]

Galacto-oligosaccharides are present naturally in human and cow's milk and are also produced from lactose by β-galactosidase. Feeding 2.5 g, 5 g, or 10 g of galacto-oligosaccharides to volunteers resulted in a dose-related increase in fecal bifidobacterial excretion, although stool weight and frequency did not change noticeably.[28] At present, no clinical studies on the use of prebiotics to prevent diarrhea have been reported.

Table 2 *Physiological importance and health benefits claimed for nondigestible oligosaccharides*

Physiological effects	Health factors
Stimulated carbohydrate metabolism in colonic bacteria; increased bacterial cell mass, short-chain fatty acids, and fermentation gases	Through short-chain fatty acids, they provide energy sources for the colonic epithelium and control of differentiation. Flatulence may be a problem. Laxative effects
Selection of bifidobacterial and lactic acid bacterial growth in large bowel	Enhanced resistance to invading pathogens
Not hydrolyzed by oral microorganisms	Protection against caries
Not glycemic	Potentially useful for people with diabetes
Nonspecific stimulation of immune function	Resistance to infection
Modulation of carcinogen metabolism	Anticancer properties
Reduced hepatic synthesis of very low density lipoprotein cholesterol and serum triglycerides	Coronary heart disease
Increased absorption of Mg and Ca	Osteoporosis

Antimutagenic activities

Probiotics and prebiotics seem to be antimutagenic in several ways. Gram-positive and gram-negative bacteria bind to mutagenic pyrolysates produced during cooking at high temperatures, and studies with lactic acid bacteria show that they can be living or dead, since the process occurs by adsorption of mutagen to carbohydrate polymers in the cell wall.[29] Lactobacilli also degrade carcinogens such as *N*-nitrosamines, which may be important if the process occurs at the mucosal surface.[30] Coadministration of lactulose and *B longum* to rats injected with the carcinogen azoxymethane reduced intestinal aberrant crypt foci, which are preneoplastic markers.[31] Purified bifidobacterial cell walls have antitumor activities in that the cell wall of *B infantis* induces activation of phagocytes to destroy growing tumor cells.[32] Bifidobacteria probiotics reduced colon carcinogenesis induced by 1,2-dimethylhydrazine in mice when used with fructo-oligosaccharides[33] and inhibited liver and mammary tumors in rats.[34] When Neosugar (4 g/day; fructo-oligosaccharides) was given to healthy volunteers in the form of chewable tablets, it increased the intestinal bifidobacteria and reduced appreciably the fecal activities of enzymes involved in producing genotoxic metabolites such as β-glucuronidase and glycocholic acid hydroxylase,[35] indicating the potential of prebiotics and probiotics to reduce or prevent carcinogenesis.

Immunity

Colonic microbiota affect mucosal and systemic immunity in the host.[36] Intestinal epithelial cells, blood leukocytes, B and T lymphocytes, and accessory cells of the immune system are all implicated.[37] Bacterial products with immunomodulatory properties include endotoxic lipopolysaccharide, peptidoglycans, and lipoteichoic acids.[38] Lipoteichoic acids of gram-positive bacteria such as bifidobacteria possess high binding affinity for epithelial cell membranes and can also serve as carriers for other antigens, binding them to target tissues where they provoke an immune reaction.[39] Yogurt lactobacilli bind in vitro to peripheral blood CD4 and CD8 T lymphocytes but not to B cells; lactobacilli that adhere to human intestinal epithelial cells are capable of activating macrophages.[40,41]

There are as yet no experimental data to support the immunostimulatory properties of nondigestible oligosaccharides in humans. Probiotic organisms interact with the immune system at many levels, however, including cytokine production, mononuclear cell proliferation, macrophage phagocytosis and killing, modulation of autoimmunity, and immunity to bacterial and protozoan pathogens.[36,37,42,43]

In vitro, bifidobacteria induce formation of large amounts of IgA.[44] Of 120 strains tested belonging to a number of species (*B animalis, B longum, B breve*), three *B breve* strains and one *B longum* isolate induced appreciable synthesis of IgA. This was confirmed in vivo when mice given one of the *B breve* strains together with cholera toxin had augmented immune responses in lymphoid tissue associated with the gut. In mice, *B breve* fed in fermented milk induced macrophagelike cells in Peyer's patches to release a factor that stimulated mitosis in B cells and enhanced production of antibodies against food allergens and pathogens.[45]

L acidophilus and *B bifidum* given in capsule form to elderly people effected appreciable changes in inflammatory and immunological responses.[46] They reduced

colonic inflammatory infiltration considerably but did not affect the numbers of B lymphocytes and T lymphocytes. Study subjects had a greater increase in B cells in peripheral blood than did controls, however. Lactobacillus GG was used to manage an allergy to cow's milk and atopic eczema in 31 infants aged 2 to 16 months.[47] It resulted in a considerable improvement in their condition and reduced fecal excretion of α_1-antitrypsin and tumor necrosis factor-α through "an improvement in antigen elimination by the gut mucosal barrier."[47]

Conclusions

We are entreated to buy the yogurts with live cultures on sale in supermarkets with promises that they will boost our body's natural resistance, promote healthy digestion, and improve the balance of our gut microflora—effects to be achieved thanks to probiotic bacteria. Even more remarkable is the suggestion that some dietary carbohydrates can selectively stimulate growth of these organisms when they occur naturally in our gut and thus produce the same benefits. If true, this is one of the most important stories to emerge in nutrition and gut microbiology since the turn of the century.

Although there are now many published reports on the use of probiotics in humans, information on prebiotics is more limited. Consequently, many of the health claims made in relation to these substances are unsubstantiated. The ability to target specific organisms in the large intestine for defined, health-promoting purposes will clearly be of great value and needs to be developed. There are considerable differences in bacterial carbohydrate utilization patterns, however, between strains as well as species,[48] which is particularly important for the development of prebiotics. A few strains have been identified as having health-promoting potential in vivo, but nonspecific increases in total bifidobacterial or lactobacillus numbers in the large bowel through the introduction of "functional foods" will probably be of questionable benefit to health.

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Complementary and alternative medicine in cardiovascular disease: what is the evidence it works?

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Despite advances in prevention and treatment over the past 20 years, cardiovascular disease remains a leading cause of death and disability. This article reviews coenzyme Q10, hawthorn, complementary chelation, and ginkgo biloba, some of the most common treatments patients ask about and use for cardiovascular diseases.

Summary points

- Coenzyme Q10 and hawthorn merit further investigation to determine what benefits, if any, they offer beyond best present therapies for cardiac ischemia and heart failure.
- The few studies of best design do not support the use of chelation therapy for cardiovascular disease.
- Ginkgo biloba is at least as effective as pentoxifylline for treatment of claudication, and further investigation, perhaps in combination with exercise, is warranted.
- Dietary supplements manufactured in the United States are of inconsistent purity and potency, making it difficult for physicians to advise their patients about how to purchase and use them.

Methods

For Coenzyme Q10 and hawthorn, MEDLINE, BIOSIS and Cochrane databases were reviewed along with references of retrieved articles and personal files of the author. Languages were restricted to English and German. Articles discussed reflect often cited references, not an exhaustive review. The discussion of chelation therapy summarizes a review of studies identified using MEDLINE (1966–1996) and CISCOM (1996) bibliographies of relevant papers and suggestions from six experts and national societies. For the *Ginkgo biloba* for peripheral vascular disease, literature searches located eight randomized placebo-controlled double-blind trials that met inclusion criteria.

Coenzyme Q10

Coenzyme Q10 is used widely in Japan, Europe, and elsewhere for a variety of purposes, but especially for cardiac disease. It is a fat-soluble, vitamin-like substance, structurally similar to vitamins E and K. It is one of many agents called ubiquinones, so named because of their presence in almost all cells of the human body. Its endogenous forms serve as essential cofactors and participate in ATP production within the mitochondria, oxidative phosphorylation, and antioxidation in membranes.[1]

Coenzyme Q10 is undergoing investigation as a treatment for diverse disorders such as Parkinson's disease and mitochondrial myopathies and for its effects on lipoprotein (a).[2-4] One of its most common uses, however, is as adjunctive therapy in the treatment of cardiovascular disease, where it has been studied for improvement of left ventricular pump function and reduction of the signs and symptoms of ischemia. A recent MEDLINE search (July 1999) for the term

"coenzyme Q10" revealed 780 articles, yet only recently has investigation focused on clinical outcomes.

In 1985 a randomized double-blind placebo-controlled crossover trial of 12 patients with stable angina pectoris used multistage treadmill exercise tests to evaluate the frequency of angina, nitroglycerin consumption, and exercise time to defined ST-segment depression.[5] Both the time until ST-segment depression and total exercise time increased significantly with coenzyme Q10, whereas there were trends to a fall in the frequency of angina at rest and nitroglycerin consumption in the treated group compared to controls. No comparison of the postrandomized groups was offered.

Nitroglycerin was the only cardioactive medication allowed. Two points that could lead to underestimation of treatment were the small number of patients and the relatively small dose of coenzyme Q10 (50 mg tid). Also of concern was the lack of a washout period between treatment and placebo. Lastly, increased serum coenzyme Q10 levels related significantly to the increased exercise duration; and ST-segment depression, heart rate, and pressure-rate product showed no differences at the same and maximal workloads. No patients dropped out; one treated patient reported loss of appetite. The authors suggest that coenzyme Q10 may be a safe and promising treatment for angina pectoris.

Chello et al. studied the effects of oral coenzyme Q10 taken perioperatively on reperfusion injury associated with coronary artery bypass grafting.[6] They randomly divided 40 patients undergoing elective surgery to a coenzyme Q10 group (150 mg/day) or control group, presumably receiving routine care only. The study was not completely blinded. They sampled arterial and coronary sinus concentrations of creatine kinase and other indicators of ischemia at several intervals perioperatively. They also observed incidence of postoperative ventricular arrhythmias and dopamine requirements. The authors report significantly lower enzyme levels in the treated group, along with significantly fewer arrhythmias and lower doses of dopamine required for inotropic support.

The authors conclude that coenzyme Q10 pretreatment inhibits perioperative lipid peroxidation, possibly decreasing sensitivity of the sarcolemma to ischemic challenge and reducing complications as noted.

A 1993 study by Morisco et al. randomized 641 patients with New York Heart Association (NYHA) functional class III and IV to receive placebo or coenzyme Q10 (2mg/kg/day) in a one-year double-blind trial.[7] They reported significantly fewer hospitalizations for worsening heart failure in the treatment group and significantly fewer episodes of pulmonary edema or "cardiac asthma." Randomization was computer generated and most patients were already taking digoxin, angiotensin converting enzyme, or diuretics.

In 1998 Singh et al. reported protective effects of coenzyme Q10 in patients with acute myocardial infarction if given within 3 days of onset of symptoms and continued for 28 days.[8] They randomized 73 patients to coenzyme Q10 (60 mg bid) and 71 patients to placebo. The authors reported a significant decrease in angina pectoris, total arrhythmias, left ventricular function, cardiac deaths, and nonfatal infarction in the treated group compared to placebo.

The study was generally well designed. No patients on entry used beta blockers, and the coenzyme Q10 group had significantly more current smokers and patients using nifedipine.

A recent study by Watson et al. evaluated quality of life (using the Minnesota "Living With Heart Failure" questionnaire), right heart pressures, cardiac output, and echocardiographic left ventricular volumes at baseline and after treatment phases of coenzyme Q10 or placebo.[9] Thirty patients with ejection fraction 26 +/– 6% were randomized to a double-blind crossover trial, with 3-month phases and 1-week washout in between phases. Notably, patients were clinically stable on the maximum tolerated doses of angiotensin-converting enzyme (ACE) inhibitor therapy; 24 were taking digoxin, 28 furosemide, and 25 hydralazine and/or nitrates. The authors found no improvement in resting left ventricular systolic function or quality of life in the coenzyme Q10 group despite a twofold elevation of serum drug levels.

The study was small but generally well designed. Patients were recruited from a heart failure and transplant unit.

Other studies have reported the benefits of coenzyme Q10 for improved inotropy, vasodilatation, exercise response, and NYHA class,[10-12] but they have often been limited by sample size, study design, or methods of measuring left ventricular response. Coenzyme Q10 has greatest bioavailability in a soybean oil preparation, and the usual oral dose varies from 100 mg to 600 mg daily in two or three divided doses. It has been well tolerated in clinical studies, with no serious side effects and infrequent reports of nausea, loss of appetite, epigastric discomfort, and diarrhea.[13] Of concern, however, are recent reports of a possible association between coenzyme Q10 and decreased responsiveness to warfarin.[14,15] Compared to other dietary supplements, coenzyme Q10 is expensive. Whether coenzyme Q10 offers benefit beyond present therapy is unknown. Clearly it should not be used in place of conventional treatments that have demonstrated effects on cardiac function and long-term outcome, but it deserves further evaluation as a safe adjunct in the management of cardiac disease.

Hawthorn

Hawthorn is commonly prescribed in Germany for New York Heart Association Class I and II patients. The flowers, leaves, bark, and red fruit all have been used for medicinal purposes. They contain oligomeric procyanidins and flavonoids[16] that may affect the heart in part by inhibition of angiotensin-converting enzymes.

Chinese herbal literature records early use of hawthorn species for a variety of medical problems, and hawthorn was observed to be of benefit for dropsy in 17th-century England. It has been recorded in numerous herbal pharmacopoeia but is notably absent from recent literature reviews.[17,18] There are few summaries of the present knowledge base regarding hawthorn.[19,20]

Schmidt et al. studied 78 patients in a randomized double-blind placebo-controlled trial of hawthorn versus placebo.[21] They evaluated the patients' working capacity by bicycle ergometry at the onset of the trial, at 28 days, and at 56 days. They also noted blood pressure, heart rate, and clinical symptoms as reported by the patients. This study was important because it used a larger dose of hawthorn (600 mg/day) than similarly designed studies with less impressive results. The randomization and blinding processes are clear and well described, and the study's few dropouts are itemized and probably of no relevance. The patients were not allowed to take ACE inhibitors, beta-blockers, calcium antagonists, long-acting nitrates, cardiac glycosides, or other cardiac medications (except long-standing diuretics) during the study.

The authors found significant improvement in maximal work capacity in the treatment group versus placebo, and work capacity continued to improve throughout the study. Clinical symptoms (fatigue, dyspnea, lack of vitality) also improved significantly and were accompanied by reduction of the systolic blood pressure (with no change in diastolic) and decrease in heart rate. The medication was well tolerated. It would be helpful to know patient beliefs about whether they were receiving treatment or placebo, and whether they participated in other exercise outside of the study.

Most of the research on hawthorn has been performed in Germany, and results from a number of randomized double-blind placebo-controlled trials of variable quality have been published. A review from 1996 summarized eight placebo-controlled trials of hawthorn for congestive heart failure (NYHA I-III).[22] All of these studies showed benefits beyond placebo and no more adverse events than placebo. It was concluded that "crataegus is an effective and safe treatment for this indication."

Whether hawthorn can offer benefit in addition to or beyond current best treatment with conventional therapy (ACE inhibitors, beta-blockers, etc.) is not known. There are no long-term outcome data to compare cardiac events, for example. Hawthorn probably has less inotropic effect than digoxin, but it also has an excellent safety record. Excessive doses are associated with hypotension and sedation.[13] Patients who choose to use hawthorn in addition to digoxin should be closely monitored to avoid overdose.

Chelation therapy

So-called "chelation therapy" for cardiovascular disease has long been a source of controversy. Numerous lay books advocate its effectiveness in treating systemic atherosclerosis, and patients often speak of it enthusiastically.[23,24] It is advocated as an alternative to revascularization procedures, available in hundreds of clinics around the country, and practiced by physicians who may belong to organizations such as the American College for Advancement in Medicine or the American Board of Chelation Therapists. Patients generally undergo one to three intravenous treatments per week for up to 40 sessions, at a total cost of $3000 to $5000.

When given intravenously, ethylene diamine tetraacetic acid is known to extract minerals from the circulation. There is no in vitro or in vivo evidence to support the contention that atherosclerosis is improved with chelation therapy through regression of calcium-laden plaques.

Numerous unblinded and uncontrolled studies have been performed, many of which claim decreased symptoms of ischemia and claudication after treatment.[25] Proper randomization, blinding, and controls are crucial, however, as many vascular disease and postmyocardial infarction patients are highly motivated to improve their diets, increase exercise, and alter stressful lifestyles, all of which may affect the course of disease. For example, in one study of chelation for peripheral vascular disease, 60% of the control group reported improvement in walking distance.[26]

A 1997 review of the few available randomized double-blind placebo-controlled trials of chelation for peripheral vascular disease did not support the results of poorly designed studies. Three trials (four papers) were analyzed. Outcomes evaluated included walking distances, ankle/arm blood pressure, angiogram results, and transcutaneous oxygen tension. The trials included 10, 153, and 30 patients, and none showed efficacy beyond placebo.[27]

Only two randomized controlled trials relating to chelation for coronary heart disease are available.[28,29] Both show no benefit in terms of objective signs or subjective improvement over and above placebo.

Chelation has been associated with causing renal problems, hypocalcemia, and death. Long-term consequences of chelation, such as possible osteoporosis, are unknown. There is presently little data and minimal theoretical basis to support randomized controlled trials.

Ginkgo biloba

In the United States, *Ginkgo biloba* is presently one of the most popular herbal remedies. It has a multitude of pharmacological effects, with a potential for alleviating circulatory problems.[30] It is licensed in Germany for the treatment of intermittent claudication. A systematic review of all randomized placebo-controlled double-blind trials on the subject summarized the evidence of eight trials that met inclusion criteria.[31] Four of them showed a significant difference in the increase of painfree walking distance in favor of ginkgo (weighted mean difference: 36.6 meters, 95% CI 28.8-43.9). Statistical pooling of the data yielded a weighted mean difference of 32.5 meters (95% CI 22.1-42.8). Adverse effects were infrequent, mild, and transient. Interestingly, this meta-analytic result compares favorably to that achieved in a recent meta-analysis for pentoxifylline.[32] *Ginkgo biloba* has platelet-inhibitory activity, and physicians should be wary of its use in patients taking anticoagulants.

Other approaches

The Dean Ornish program of lifestyle and dietary changes has been studied systematically and may help in the secondary prevention of cardiovascular disease.[33] Vitamin E is beginning to appear useful as adjunctive therapy for secondary coronary heart disease prevention, possibly for primary prevention, although the American Heart Association does not yet recommend its routine use.[34]

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capsule

Beware of burns from ice packs Ice packs can be just as damaging as hot water bottles if they are applied directly to the skin, warn two plastic surgeons from the UK (British Journal of Sports Medicine 1999;33:278-279). A 59 year old woman in their care sustained a partial thickness burn to the calf after a gym instructor told her to rest it on an icepack for 20 minutes. Freezing and compressing the skin at the same time is asking for trouble, they say, so always put something between the ice and the skin.

MEDICINE CABINETS

Cranberry, feverfew, horse chestnut, and kava

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A growing body of controlled clinical trials, primarily from European countries, suggest that many herbal medicines have therapeutic activity with few adverse effects. The quality of these studies is variable. Most clinical trials of herbal medicines have not received the same rigorous level of scientific scrutiny as have drugs that have been approved by the Food and Drug Administration (FDA) in the United States. Dose-response studies are almost nonexistent and few herbal medicines have been compared to standard doses of conventional pharmaceutical drugs. Methodologic study weaknesses, publication bias, and contrasting results of studies contribute to disagreements and skepticism in interpreting herbal literature. The following four herbal medicines (among many others) have potential benefits supported by randomized controlled trials reported in US or European literature.

CRANBERRY (*Vaccinium macrocarpon*)

Long used by patients to help prevent urinary tract infections, cranberry juice was once thought to work by acidifying the urine or by the excretion of hippuric acid. It is now known that specific proanthocyanidins, chemicals found in cranberries (as well as blueberries), inhibit the adherence of *E coli* to urinary tract epithelial cells.[1,2]

Controlled trials

Two preliminary US randomized controlled trials suggest that there may be clinical benefits with cranberry products. In one well-designed, double-blind placebo-controlled study, investigators gave 300 ml/day of cranberry juice cocktail (supplied by Ocean Spray Cranberries, Inc.) or a placebo beverage to 153 elderly female nursing home residents over a 6-month period.[3] Pyuria with bacteriuria was significantly reduced in the cranberry (15%) versus placebo (28.1%) group (P=0.004). Antibiotics for urinary tract infections were prescribed eight times in the cranberry group and 16 times in the placebo group by the patients' own physicians.

AP Photo/Daniel Hulshizer

Cranberries

In a much smaller double-blind placebo-controlled trial, with a crossover design over 6 months, investigators gave a daily cranberry extract capsule (supplied by Solaray, Inc.) or a placebo to 19 young, sexually active women (median age 37) with recurrent urinary tract infections.[4] Nine people were lost to follow-up due to pregnancy, moving out of the area, or other infections requiring antibiotics. Of the remaining 10 patients, while taking the cranberry product, seven had reduced frequency of clinical urinary tract infections, one person had one more urinary tract infection, and two people had no change in their frequency of infection. Of 21 incidents of urinary tract infections, 6 occurred while taking the cranberry product and 15 occurred while taking placebo, a statistically significant difference (P<0.005).

Adverse effects and administration

There are no known adverse effects of cranberries. Doses in the clinical trials included 300 ml/day of a standard cranberry juice cocktail beverage, in single or divided doses, or a daily 400-mg dietary supplement capsule.

Conclusion

Physicians can consider cranberry products to be a safe prophylactic therapy that may help reduce the frequency of urinary tract infections in susceptible individuals. Cranberry's prophylactic activity compared to antimicrobial drugs and cranberry's effects on acute urinary infections have not been investigated.

FEVERFEW (*Tanacetum parthenium*)

Commonly used for headaches, feverfew has also been used for arthritis, menstrual discomfort, and a variety of other disorders. Pharmacologically, feverfew may inhibit prostaglandin synthesis and histamine release from mast cells, affect platelet activity, and/or inhibit vascular smooth muscle contractility.[5,6]

Controlled trials

Four randomized controlled trials from outside the United States have studied feverfew for the prophylaxis of migraine headaches; three of those studies found beneficial results compared to placebo. In a small British double-blind placebo-controlled study, investigators studied 17 patients who regularly ate feverfew leaves for self-prophylaxis of migraines.[7] Switching patients to a placebo caused a significant increase in migraine symptoms compared to symptoms in patients who continued with a feverfew capsule preparation. Other British investigators randomized 76 migraine patients in a double-blind placebo-controlled study with a crossover design lasting 8 months.[8] Feverfew (70- to 114-mg/capsule of powdered dry leaf daily) significantly decreased the num-

ber of attacks (3.6 vs 4.7 attacks/2-month period, P<0.005) and decreased symptoms of nausea and vomiting compared to a placebo (P<0.02). There was a nonsignificant trend toward milder headaches (P=0.06), and the duration of individual attacks was not reduced. However, 16 patients did not complete the study, which was not taken into account with intention-to-treat analysis. An Israeli double-blind placebo-controlled crossover trial of 57 migraine patients, lasting 4 months, demonstrated that feverfew (100-mg capsule of powdered dry leaf daily) significantly decreased pain, vomiting, and sensitivity to light and noise compared to a placebo (P<0.01).[9]

In contrast, a Dutch randomized double-blind placebo-controlled crossover study found that feverfew in a dose of 143 mg/day was no better than a placebo.[10] Fifty migraine patients took a specific ethanolic feverfew extract (as opposed to powdered dry leaf) that was standardized to parthenolide. This chemical was previously considered to be an active component of feverfew but had never been confirmed clinically. The negative findings of this study may be the result of standardizing to the wrong chemical entity, as parthenolide may not be the active constituent. None of the three crossover studies had adequate washout periods.

In a separate double-blind placebo-controlled study, using a dose of 70- to 86-mg/day of encapsulated dried leaf, feverfew was found to be ineffective for the treatment of rheumatoid arthritis.[11]

Adverse effects and administration

Feverfew use is associated infrequently with mouth ulceration or inflammation, mild gastrointestinal disturbances, and contact allergy to the plant,[6] but reported side effects from the clinical trials were no different than placebo. The feverfew plant can cause abortions in cattle and is therefore contraindicated during pregnancy.[6] Feverfew may affect platelet activity in vitro, but there have been no reported cases of laboratory abnormalities, bleeding, or adverse interactions with anticoagulant or antiplatelet drugs. The dose used in successful controlled trials was approximately 50 to100 mg QD of encapsulated dried leaf preparations.

Conclusion

Physicians can consider feverfew to be a relatively safe herbal medicine that may be beneficial for migraine headache prophylaxis. Feverfew has not been compared to standard pharmacologic prophylaxis in controlled trials, nor has it been investigated or is it recommended for treatment of acute migraine attacks.

HORSE CHESTNUT (*Aesculus hippocastanum*)

Traditionally used for arthritis and rheumatic complaints, a standardized horse chestnut seed extract is extremely popular and has been well-studied in Europe for treating chronic venous insufficiency. It has also been promoted as a topical treatment for varicose veins and hemorrhoids. Horse chestnut seed extract has been shown to decrease venous capillary permeability in pharmacologic studies.[12,13]

Controlled trials

A recent systematic review of worldwide literature found 13 randomized controlled trials, all double-blinded, that fulfilled a majority of standard inclusion criteria to reduce bias.[12] None of these trials, however, was completely flawless. Eight studies were placebo-controlled and five were controlled against another European phytotherapy agent. Studies lasted between 2 and 12 weeks. In all eight placebo-controlled studies, horse chestnut seed extract significantly decreased the symptoms of chronic venous insufficiency (leg pain, pruritus, feeling of leg fatigue or tenseness) or decreased leg volume and edema, compared to placebo (P-values all <0.05). Although not adequately blinded, one study found horse chestnut seed extract to have similar benefits to compression stockings.[14]

Adverse effects and administration

Ingestion of high doses or parenteral administration of horse chestnut preparations may be toxic; renal, hepatic, and hematologic abnormalities have been reported rarely.[15] The side effects of the processed extract are generally similar to placebo, however, with reports of mild gastrointestinal symptoms, headache, dizziness, and pruritus in less than 3% of patients.[12] Standardized horse chestnut seed extract contains 16% to 20% triterpene glycosides, calculated as aescin (or escin), which is considered the main active constituent. The usual recommended daily dose is 100 to 150 mg of aescin equivalent, or about 500 to 750 mg of horse chestnut seed extract that contains 20% aescin. In the clinical trials, the most common dose was 50 mg of aescin (about 250 mg of horse chestnut seed extract) bid, using a commercial preparation that is now marketed in the United States (Venostat, by Pharmaton/Boehringer Ingelheim).

Conclusion

Horse chestnut seed extract is a safe herbal medicine that may be useful for the treatment of chronic venous insufficiency. Benefits have not been adequately compared to standard therapies such as compression stockings or diuretics, but there is little reason why it cannot be tried as an adjunctive or alternative therapy.

KAVA (*Piper methysticum*)

A beverage made from the root of the kava plant has been used for centuries by South Pacific islanders as an integral part of their culture, both ceremonially and socially, with relaxing or calming properties.[16] Specific kava extracts have been studied in Europe and are widely marketed in solid dosage forms to treat symptoms of anxiety, stress, or ten-

sion, without causing cognitive disturbances. The active constituents, kava pyrones (also called kava lactones), have experimentally been found to have skeletal muscle relaxant, anticonvulsant, and local anesthetic properties.[13,16]

Controlled trials

Five randomized double-blind placebo-controlled trials of kava extract products have been published in Europe.[17-21] Studies included 40 to 100 patients each and lasted from 1 to 6 months. Two studies included women with primarily perimenopausal complaints, while the others included patients with a variety of different anxiety disorders. All studies, using several objective anxiety rating tools, found that kava reduced anxiety symptoms compared to placebo. Effects were usually observed within one week (the first measurement point in the studies), but the longest trial found effects to be statistically significant only after 2 months.[21] After 6 months, withdrawal effects were reportedly not observed when therapy was discontinued after a one-week placebo washout. One European randomized double-blind comparative trial of 172 patients found beneficial results similar to that of relatively low-dose benzodiazepines (oxazepam 15 mg/day and bromazepam 9 mg/day).[17,22]

A separate randomized double-blind placebo-controlled trial conducted with a US dietary supplement (Kavatrol, by Natrol) studied kava's effects on mild day-to-day stress for one month in 60 patients. The investigators report beneficial effects, but results are currently published only in abstract form.[23]

Adverse effects and administration

Mild side effects such as gastrointestinal discomfort, headache, dizziness, and allergic skin reactions have been reported in less than 2.3% of patients in open studies and were generally similar to placebo in the controlled trials.[13] A variety of studies using EEG and psychometric tests suggest that European kava preparations, unlike benzodiazepines, do not affect intellectual and motor functioning.[13,24,25] A kava dermopathy characterized by yellowing of the skin and scaly dermatitis is common in chronic heavy kava drinkers in the South Pacific; the effects are reversible after discontinuation of the herb.[26]

A few serious adverse effects have been occasionally associated with kava use. Traditionally prepared kava beverages, especially with excessive doses, may produce an effect similar to depression of the central nervous system.[27,28] One 44-year-old US motorist was arrested for intoxication after appearing to be drunk, but with no evidence of alcohol use, presumably after drinking 16 cups of a kava beverage.[29] There are three reports of extrapyramidal-like dystonic reactions and one case of worsening Parkinson's disease, mostly from European kava preparations.[30,31] Severe disorientation has been reported in a patient using a US kava supplement in conjunction with alprazolam and cimetidine.[32]

The usual therapeutic dose of kava is about 140 to 250 mg/day of the kava pyrone constituents, in 2 to 3 divided doses. In the US clinical trial, two tablets containing 60 mg each (120 mg kava pyrones total) were given twice a day. In the European clinical trials, the usual dose was 70 mg three times a day of kava pyrones (100 mg tid of a specific extract product). This European product (WS 1490) is manufactured according to strict guidelines and is usually standardized to include 70% kava pyrones. In contrast, US supplements vary widely among brands, with kava pyrone content usually between 30% and 55%. Consumers should read the labels carefully.

Conclusion

Kava may be a beneficial herbal medicine for mild stress or anxiety, with minimal abuse potential. However, the potential for adverse effects from doses higher than recommended and drug interactions are concerning. The relative efficacy of kava compared to usual doses of standard antianxiety drugs is not known. Kava is contraindicated in patients with Parkinson's disease. It would also be prudent, until effects are better known, to avoid kava in patients taking drugs with extrapyramidal side effects or who are taking central nervous system depressants such as benzodiazepines or alcohol.

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Echinacea in the treatment and prevention of upper respiratory tract infections

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Introduction

An estimated $21.2 billion was spent on complementary medicine in 1997.[1] Echinacea, the top-selling herbal product in the United States, is at the forefront of the herbal revolution, with annual sales estimated at more than $300 million. The German Commission E lists that echinacea preparations "support and promote the natural powers of resistance of the body, especially in infectious conditions of the nose and throat."[2]

The objective of this analysis is to describe the pharmacology and clinical evidence for echinacea in the treatment and prevention of upper respiratory tract infections.

Historical use

Extracts, teas, tinctures, tonics, tablets, and ointments containing various parts of the echinacea plant (family Compositae) have been used since the 1600s by Native Americans. Tribes including the Cheyenne and the Crow used echinacea for a variety of medical problems, from sore gums and coughs to bowel trouble and snakebites.[3] The popularity of echinacea as a general medical treatment did not occur until the late 1800s, when Nebraska physician H.C.F. Meyer sold a root extract of *Echinacea angustifolia* as a "blood purifier."[4,5] Meyer subsequently sent his herbal concoction to John King and John Lloyd, a prominent physician/pharmacist team involved in the eclectic medicine movement of the late 1800s. Soon Lloyd Brothers Pharmacists of Cincinnati began marketing echinacea extracts as "anti-infective agents."[3-5] The popularity of echinacea extracts remained steady through the early part of this century, and from 1916 to 1950 echinacea was included in the US National Formulary. In the 1930s, with the advent of the sulfa antibiotics, the popularity of echinacea as an anti-infective agent began to wane in the United States, and only in the past few decades has it made a comeback.

Recent clinical studies of echinacea have focused on the treatment and prevention of upper respiratory infections. Other suggested uses include alleviation or reduction of adverse effects of chemotherapeutic agents; treatment of urinary tract infections; and topical use for chronic wounds, snake and mosquito bites, and recurrent *Candida* infections.[6]

Botany and taxonomy

The word "echinacea" is derived from the Greek *echinos,* meaning "hedgehog" or "sea urchin." The name was given to the plant because of its spiky seed heads.[4] The three most common echinacea species for medicinal purposes are *E angustifolia* (narrow-leaved), *E purpurea* (common), and *E pallida* (pale). *E purpurea* is the most popular commercially cultivated species. Common names for these perennial herbs include purple coneflower, Missouri snakeroot, Indianhead, scurvy root, comb flower, hedgehog, and red sunflower.[3-7] Native to Kansas, Nebraska, and Missouri, echinacea is closely related to sunflowers, daisies, and ragweed, all members of the Compositae/Asteraceae family. The stems have a sharp tingling taste when chewed.[8] Medicinal products are prepared from the dried roots of *E angustifolia* and *E pallida*, and from the juice of the stems and flowers as well as the root of *E purpurea*.[3,6,7]

Chemistry and pharmacology

As with many medicinal plants, echinacea contains at least six distinct chemical constituents with pharmacologic activity (polysaccharides, flavonoids, chicoric acid glycosides, essential oils, polyacetylenes, and alkylamides).[3-7] There is much controversy and confusion over which

chemicals present in echinacea are responsible for its activity. The three main species differ slightly in composition, and other factors such as the method of extraction, the time of year of harvest, and the part of the plant used can significantly affect the quantity of active ingredient(s) present.[4,5,7] The polysaccharide, alkylamide, and chicoric acid glycoside components are believed to provide most of echinacea's nonspecific immunostimulatory activity.

A number of polysaccharides with pharmacologic effects on the immune system have been isolated. Heteroxylan is a high-molecular-weight polysaccharide that activates phagocytosis. Arabinogalactan functions to promote the release of tumor necrosis factor and increases production of macrophage interleukin-1 and interferon beta-2.[6,8,9] Alkylamides and chicoric acid glycosides also appear to stimulate phagocytosis. Echinacein is an isobutylamide that is responsible for echinacea's pungent smell and distinct taste.[8,9]

While echinacea does not appear to have any direct antibacterial or antiviral activity, it appears to exert beneficial effects through immune system modulation, thus indirectly providing an "anti-infective" effect. Most studies investigating the pharmacology of echinacea have used the parenteral formulation, which is not available in the United States, and it is unclear to what degree the activity of the orally administered preparations mimics that of the parenteral formulation.[4,10]

Efficacy

Two systematic reviews have attempted to provide a clear description of the available literature.[11,12] Prior to these reviews, most echinacea clinical trials were in German, and not readily accessible. The first systematic review of clinical trials addressing echinacea's effects on immunomodulation evaluated a total of 26 clinical trials. Of those, only six used products containing echinacea as a sole component of the tested extract, and only three addressed the use of echinacea in the treatment or prevention of upper respiratory tract infections.[11,14,15] Recently two clinical trials investigating the use of echinacea in the prevention of upper respiratory infections were published in English.[13,14]

Braunig et al. conducted the two studies evaluating echinacea in the treatment of acute respiratory tract infections.[11,15,16] The first randomized controlled trial investigated the efficacy on reduction of length of illness of *E pallida* root extract 900 mg (90 drops) daily for 8 to 10 days versus placebo in a total of 160 patients with acute upper respiratory tract infection.[11,16] Patients treated with the echinacea extract had a significantly shorter duration of illness (13 vs 9.8 days, P<0.001). The second trial evaluated the use of *E purpurea* root extract at two different doses (450 mg [90 drops] or 900 mg [180 drops]) with placebo in 180 patients.[11,15] Patients taking the higher dose of extract fared significantly better than the placebo and low-dose groups in terms of cold symptoms evaluated at 3 to 4 and 8 to 10 days (P<0.0001). This study suggests the effects of echinacea in the treatment of upper respiratory tract infections are dose-dependent. It is unclear in the review of each of these trials if the treatment and placebo were initiated at the same point in the course of the acute upper respiratory tract infections in all patients.[11]

A-Z Photos/Robert Erwin

Echinacea

The prevention trial conducted by Schoneberger et al. evaluated the use of pressed juice of *E purpurea* at a dose of 4 ml twice daily for 8 weeks versus placebo in 108 patients with a history of more than three upper respiratory infections in the previous six months.[11,17] The treatment group had a nonsignificant decrease in number and length of subsequent upper respiratory infections when compared with the placebo group.

Studies of echinacea in the prevention of upper respiratory tract infections have been published in the past year in English-language journals.[13,14] Melchart and colleagues evaluated the use of 50 drops of ethanolic extracts of *E purpurea* and *E angustifolia* root or placebo given twice daily for five days each week for 12 weeks in a three-armed randomized double-blind trial in 289 patients.[13] The primary outcome measure was the time taken to develop an upper respiratory tract infection. In the intent-to-treat analysis, no significant differences were found between the three groups in the mean number of days to the development of an upper respiratory tract infection, the percentage of patients with one or more infections, and the number of participants reporting adverse effects. The only significant result was that more patients in the two echinacea groups believed they had received benefit from their treatment (P=0.04), possibly due to problems with blinding the echinacea extracts. This study did not report concurrent use of echinacea in other forms or other pharmacologic agents (allopathic and complementary) that may potentially have an impact on the incidence and/or severity of upper respiratory tract infections. It is also nearly impossible to blind patients to the echinacea extracts due to their characteristic taste. Overall, limitations present in the available clinical trials include the different doses and different species of echinacea used in

each trial, different methods of extraction used in preparation of the tested medicinals, relative lack of standardization of initial diagnosis of upper respiratory tract infection, and frequent use of combination products.

The most recent prevention study was conducted by Grimm et al. in patients with a history of more than three colds or respiratory infections in the preceding year.[14] One hundred nine patients were randomly assigned to take either 4 ml fluid extract of *E purpurea* (from the whole flowering plant without roots and containing 22% alcohol) or 4 ml of alcohol/water solution twice a day for 8 weeks. There was not a significant difference between groups in terms of the incidence, duration, or severity of upper respiratory tract infections.

Safety and tolerability

Detailed assessments of adverse effects of herbal products are often not reported in clinical trials. Such is the case with many echinacea clinical studies. The German Commission E monographs state there are no known side effects with the oral and topical use of these agents.[2] Parenteral use has resulted in fever, elevations in white blood cell counts and blood glucose, nausea, and vomiting.[2] Adverse events detailed in the Grimm trial included mild and transient central nervous system and gastrointestinal effects that occurred at similar rates in the treatment and placebo groups.[14] Similar numbers of patients in each group withdrew from the study, most commonly because of the poor taste of the study medication and gastrointestinal effects. A similar adverse event and withdrawal pattern was seen in the Melchart et al. trial.[13]

A theoretical concern exists for cross-sensitivity of echinacea in those patients allergic to other members of the Compositae/Asteraceae family. A single case of echinacea-associated anaphylaxis (chest tightness, burning of the mouth and throat, and generalized urticaria) has been reported in the literature, in a woman with a history of multiple food and plant allergies.[18] Subsequent skin testing revealed allergy to echinacea extract and ragweed. Patients with known allergy to these plants (including daisies, sunflowers, and ragweed) should be cautioned regarding the use of echinacea products.

Echinacea does contain small amounts of pyrrozolidine alkaloids, but concern regarding pyrrozolidine-associated hepatotoxicity is not warranted, due to structural differences in these alkaloids that render them nontoxic compared with other known hepatotoxic pyrrozolidine alkaloids.[5,19] A general recommendation against the use of herbal products in patients with poor hepatic and/or renal function would be prudent, given the lack of safety information regarding use by these populations.

Combining echinacea products with known immunosuppressants should be avoided if possible, due to the possibility of a significant pharmacodynamic drug interaction.[19] The German Commission E states that the use of echinacea should be avoided in patients with any "progressive systemic immune disease" such as lupus, HIV infection or AIDS, or multiple sclerosis and in patients who have undergone organ transplantation or who are on immunosuppressants.[2] The use of echinacea should also be avoided in pregnant and lactating women until more information is available.[2] Echinacea should not be taken orally for more than 8 weeks because of the potential for decreased immune response with continuous use.[2]

Price

The cost of single-agent echinacea preparations varies widely, depending on manufacturer, echinacea content, species of echinacea, and dosage form. Capsules range from five to 75 cents apiece, liquid extracts from 25 to 35 cents per milliliter.[20]

Recommendations for clinical practice

Although echinacea appears to be safe in most patients, more clinical studies are needed to assess its efficacy. As evidenced by the studies detailed in the preceding section, the appropriate dose and most effective formulation of echinacea are not known. The German Commission E recommends 900 mg of *E pallida* root, or 6 to 9 ml of expressed juice of *E purpurea* herb.[2] For acute infections, a dose of 300 to 400 mg of a dry extract three times daily has been advocated.[3]

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CURBSIDE CONSULT

Marvin Honeycutt

Where can I find quality information about herbal and other complementary medicines?

Quality information on herbs is often not in English, not based on human data, and not of high quality when human subjects are used. There is, however, a growing body of evidence-based literature in peer-reviewed journals. This is a constantly changing field. New articles and Web sites are appearing on a regular basis.

There are a variety of books, newsletters, and databases for physicians and here are the ones that provide the highest quality information and are the easiest for busy practicing physicians to use.

Books

Robbers J and Tyler V. Tyler's Herbs of Choice: The Therapeutic use of Phytomedicinals. New York: Haworth Herbal Press; 1998. $49.95 *****

This is a new, fully referenced, excellent general herbal guide for physicians. Varro Tyler has written a number of high-quality textbooks. The easiest to read of all the books listed here, this book is also arguably the best. It stresses the pathophysiology of certain diseases and shows the mechanism by which herbs work.

Schulz V, Hansel R, and Tyler VE. Rational Phytotherapy: A Physician's Guide to Herbal Medicine. Springer; 1998. $49.95. ****

This is an excellent, well-referenced book that includes articles and citations from non-English journals. It has an easy-to-follow format, organized by general medical symptoms and diseases, followed by discussions on herbs used for those particular diseases and organ systems. There is a thorough section on the types of herbal preparations and what they mean, including teas, tinctures, pills, and powders. The book misses several of the commonly used women's herbs that patients ask about, including cranberry and blue cohosh. Overall, however, this is one of the best sources for the physician interested in a more detailed discussion of herbal therapies and the research that has been published internationally.

Tyler V. The Honest Herbal (4th ed.). Pharmaceutical Products Press; $28.00. 1999.***

This is a good basic reference, perhaps the best to keep on hand in the office or at home for the physician who is not as interested in evidence-based herbal medicine.

Karch S. The Consumer's Guide to Herbal Medicine. Advanced Research Press; 1999. $29.99. **

The strength of this book is its excellent introduction to the current political climate in the United States concerning herbal medicine. The appendix also has an excellent section on how to do a free MEDLINE search. The book's drawback is the section on individual herbal medicines that is neither as thorough nor as clinically relevant for physicians as those in other books.

Monographs

German Commission E Monographs. $189.99 ***

These herbal monographs were translated from German to English and published in 1998. A new edition is due out this year. Recommendations for herbal therapies were formulated by a Health Commission in Germany that existed from 1978-1994. Their recommendations are based on more than just randomized controlled data. Historical and folk use of herbs, anecdotal information, case reports, and unpublished data all went into the recommendations. Major drawbacks to these monographs are their exclusion of references and their use of data up to only 1994. Information is often specific to products available only in Europe. This is not the top book to buy on herbal therapies. Purchase it through the herb education catalog from the American Botanical Council: (800) 373-7105.

The Review of Natural Products—Facts and Comparisons. $139. *****

An expensive but worthwhile purchase, these monographs on herbs are updated and published in a style similar to Scientific American's They are concise with helpful information on use and dosage, referenced with animal and human data. A subscription to yearly updates costs $139. The toll-free number is (800) 223-0554.

Newsletters

Alternative Medicine Alert. $189/year. *****

This well-researched newsletter focuses on the clinical use of alternative medicine and complementary topics and is well researched and easy to read. Articles are thorough, well referenced, but brief. This newsletter recently won a first-place Newsletter Publication Award. The newsletter also offers CME credits. More information is available at (800) 688-2421.

The Integrative Medicine Consult. $189/year. ****

This newsletter also contains excellent reviews on a variety of complementary topics. It is as expensive as Alternative Medicine Alert and does not have as many subscribers. To order, write IMC, 1029 Chestnut Street, Newton, MA 02464.

FACT/Focus on Alternative and Complementary Therapies. $89/year. ****

This newsletter, published at the University of Exeter, United Kingdom, is another great source for brief reviews of current literature and books as well as for occasional systematic reviews. More information is available from www.ex.ac.uk/FACT/. Order by fax at (212) 686-7993 or write to Pharmaceutical Press, c/o CABI Publishing, CAB International, 10 East 40th Street, Suite 3203, New York, New York 10016.

Special reports/theme issues

Various journals have dedicated entire theme issues to alternative and complementary medicine. Their articles are about not only herbal medicine but also other related topics, including homeopathy and acupuncture.

JAMA 1998 Nov 11; Arch Int Med 1998 Nov 9; Arch Neurol 1998 Nov; Arch Gen Psychiatr 1998 Nov; Arch Pediatr Adolesc Med 1998 Nov; Arch Surg 1998 Nov; Arch Fam Med 1998 Nov.

Databases

There are a number of free databases that physicians can access from their offices.

PubMed *****

http://www.ncvbi.nlm.nih.gov/PubMed/
This is MEDLINE's publicly available search service of the entire nine million-citation database. The MEDLINE-indexed journals, however, do not include a large volume of botanical scientific information.

HerbMed *****

http://www.amfoundation.org/herbmed.htm
This is a new electronic evidence-based resource for herbal information with hyperlinks to clinical and scientific publications. The site is clearly organized into six categories for each herb: evidence for activity, warnings, preparations, mixtures, mechanism of action, and other.

General Internet resources

Columbia Medical School's Rosenthal Center of Alternative and Complementary Medicine *****

http://cpmcnet.columbia.edu/dept/rosenthal/databases/AM_databases.html
This website has been organized in an easy-to-use format. Through it, you can link with PubMed and HerbMed.

University of Pittsburgh Alternative Medicine Homepage ***

http://www.pitt.edu/~cbw/altm.html
A directory of internet sites with helpful annotations. Both disease categories and specific alternative modalities, including herbal therapies, organize this site. This is a good site for locating licensed professionals for acupuncture, herbal, and other alternative therapies.

Internet information on adverse reactions
Medwatch ***

http://www.fda.gov/medwatch
Medwatch, the FDA's Medical Products Reporting Program, provides access to the Special Nutritionals Adverse Event Monitoring System, a searchable database reporting adverse effects and problems associated with the use of herbal products. Results are presented in a table, showing each product's name, manufacturer, and adverse effects.

Phytonet ****

http://www.exeter.ac.uk./phytonet
Phytonet, maintained by the Center of Complementary Health Studies at the University of Exeter, United Kingdom, is designed to keep researchers up to date with the work of the European Scientific Cooperative on Phytotherapy (ESCOP), an organization promoting the development of therapeutic standards for herbal medicines. One of Phytonet's major functions is the collection and dissemination of information on the adverse effects of herbal preparations.

On-line magazines and newsletters

HerbalGram *****

http://www.herbalgram.org/herbalgram/index.html
This herbalist magazine is published by the American Botanical Council and includes research reviews, legal issues, herb market trends, book catalogue, and features.

If you join the Herb Research Foundation, you get a subscription to HerbalGram for free. The addresses are:

American Botanical Council
P.O. Box 144345
Austin, Texas 78714-4345
www.herbalgram.org
Tel. (800) 373-7105

Herb Research Foundation
1007 Pearl Street, Suite 200
Boulder, Colorado 80302
www.herbs.org
Tel (303) 449-2265

Medical Herbalism ***

http://medherb.com/MHHOME.SHTML
A full-text clinical newsletter for the herbal practitioner. This site also links to herbal medicine databases not found easily elsewhere, such as David Hoffman's Health World Materia Medica and Grieves' Modern herbal.

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Culture and Medicine

Alternative medicine—rural style

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The growth of alternative medicine is phenomenal—the World Wide Web and computer databases offer comprehensive information, weekend seminars are available somewhere every month, innumerable books have been published, and gurus abound. Gradually and sometimes grudgingly the medical profession is acknowledging the reality of alternative medicine. Research programs to study the efficacy of alternative medicine as adjunctive care for cancer patients are now active in such centers as the Sloan-Kettering Institute in New York, Harvard Medical School, and California-Pacific Medical Center in San Francisco.

But these unconventional medical practices pose a problem for traditional physicians. Both the medical and the legal traditions in our culture demand that doctors practice "scientifically." A physician offering cure by "unproven" therapies could be subject to peer-review discipline, loss of license, malpractice lawsuits, and even criminal proceedings.

How far will advocates of alternative medicine go to integrate it into mainstream medicine? What will integration mean for smaller health facilities that cannot run large research programs but do have patients who want to try alternative therapies?

The massage therapy has dramatically improved a patient with a severe head injury and spastic paralysis.

Sierra Valley District Hospital, a small rural health facility, lies in a lush farming and ranching valley on the eastern slope of the Sierra Nevada. It has four acute beds, 33 skilled nursing facility beds, and limited X-ray and clinical laboratory services. The hospital also maintains a clinic in which about 20 patients are seen each day and offers 24-hour-a-day emergency services and selected inpatient care. All of these services are provided by a family practice of five board-certified physicians, who work on a rotating basis so that there is always one doctor in town. In a spirit of "hi-touch" rather than "hi-tech," the doctors, the administrators, and the board members of this rural hospital have set out the basis by which they will deal with the numbers of patients seeking "alternative" or "complementary" healing methods.

After much discussion, the five physicians decided to add the following statement to the preamble of the medical staff bylaws: "It is recognized that the healing services provided by the hospital are guided by a philosophy of caring, that the activities of the medical staff are a human service, and that the essence of healing is in relationship with those who are served. The intention of all services to patients and interactions between the various branches of caregiving is that of respecting the sacredness of life and the uniqueness of each human individual. It is the intent of the medical staff to provide not only physical therapeutics but to conjointly attend to the emotional, mental, social and spiritual needs of all people."

But the doctors have actually gone even further. They decided to include provisions in the bylaws for credentialing and granting of medical staff privileges for "alternative" or "complementary" practitioners, so that they would have an appropriate status in the hospital with the blessings and within the purview of the medical staff. In September 1998, these changes to the bylaws were unanimously voted in by the medical staff and approved by the hospital board of directors. Since then, actual medical staff practice privileges have been granted to a certified massage therapist and to two chiropractors, one of whom is expert in homeopathy and herbal therapies and the other of whom is entering into a acupuncture licensing program. Additionally, at the request of patients or their families, temporary privileges for a period of two months have been granted to a Reiki therapist, and a series of "magnetic" therapy treatments were given to a semi-comatose patient. Provisions have been made within the rules and regulations so that the work of all therapists is coordinated through the attending physician. Quality assurance procedures have been put into effect so that alternative practices are reviewed in a manner similar to that required for traditional scientific practices.

Clearly, no statistically valid data are available to measure outcomes of these new therapeutic practices. But the anecdotal evidence is heartwarming. The massage therapy has dramatically improved a patient with a severe head injury and spastic paralysis who was not responding to muscle relaxants; it also helped a patient with dementia whose aggressive behavior was not responding to psychotropic medications and who was going to be transferred to a more secure facility. This patient is now adequately soothed by a twice-weekly relaxation head-and-neck massage. At least two patients, both of them post–multiple surgical procedures and habituated to pain medications, have found their severe lower-back pain relieved. They have been able to reduce their drug intake significantly under the care of a chiropractor who practices "polarity" and body-energy techniques together with chiropractic manipulations. In one dramatic instance, acupuncture administered by a doctor experienced in the technique resulted in immediate, and after many months seemingly permanent, cessation of smoking and absence of nicotine craving in a 46-year-old patient with extremely high risk factors for cardiovascular disease who had before been unable to overcome a 20-year-long, three-pack-a-day addiction.

The energy inherent in these medical staff activities has spread throughout the hospital. Meetings have been held with local hospice workers and clergy to discuss how better to coordinate the mind-body-spirit aspects of treating patients with serious illnesses. A series of open dialogues has been attended by members of the medical, administrative, and nursing staffs. Those meetings led to the creation of a nondenominational spiritual healing logo, an image of a dove, to be posted in various places in the hospital as a reminder of the sacred nature of healing. Currently the hospital is applying for a grant from a benevolent foundation with which to obtain audiovisual aids and materials for art therapy; to create a sacred space, a chapel, in the hospital for prayer and meditation; and to provide educational and experiential programs for caregivers to learn ways to include the spiritual in their work.

An interface between alternative medicine and traditional medicine remains speculative. Meanwhile, Rural Sierra Valley District Hospital is acting on that possibility by adopting bylaws with a clear humanistic statement about the sacredness of healing and by granting alternative medicine practitioners membership on the medical staff.

Suggested reading

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Sorcery and science: responses to kuru and other epidemics

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"I can cure kuru, " Sila told me. I had been hiking with my guides on a trail along a steep ridge in Papua New Guinea, where I was conducting epidemiological field work on kuru among the Stone Age Fore group. My guides introduced Sila and me, evidently thinking that he, their local medicine man, could instruct me how to treat kuru effectively.

I squinted at him through the glaring sun. He was barefoot, and wore a soiled pair of shorts. What could I possibly learn from him?

"How well has your treatment for kuru worked? " I asked.

He listed his patients, most of whom, he said, had recovered. Over the previous few months, I had met some of these individuals and thought they seemed healthy. He also admitted that several of his patients had worsened.

"Who?" I asked. He listed several, all of whom I had been taken to see and had diagnosed with the disease. Our lists of current kuru patients were identical. "What's your treatment?" I asked, still suspicious. I wasn't sure he would tell me.

But he answered. He said he first uttered an incantation, then dispensed herbal medicines and prescribed several behavioral changes: for one week, patients were not allowed to drink water, eat any salt, or touch anyone of the opposite sex.

Sila's confidence puzzled me. I knew that dozens of Fore herbal medicines had been tested at the National Institutes of Health and shown to be ineffective. Kuru, caused by an infectious protein or prion—virtually identical to that responsible for Creutzfeldt-Jakob disease in humans, scrapie in sheep, and bovine spongiform encephalopathy (BSE) or mad cow disease—has no known treatment in the West. Here in New Guinea, the disease had wiped out most of the population in some villages. Fore members who developed headaches, backaches, or a host of other minor pains now automatically feared they had kuru. I labeled these cases as misdiagnoses and as hypochondriacal. But presumably these same people constituted Sila's "cures" and lent credence to the Fore belief that the disease was caused—and could be cured—by magic. The tribespeople thus had an explanation they could understand, giving them some sense of control over the epidemic.

Still, none of the patients whom I had diagnosed as having kuru had responded to Sila's therapy. Why, then, didn't he see a problem or feel troubled by the ineffectiveness of his medicine? I didn't want to offend him, but I felt compelled to ask, "Why are some people whom you treat still sick?"

"Very simple, " he replied. "They didn't follow my advice. They drank water or ate salt or touched a member of the opposite sex." In short, they were noncompliant. He blamed these failures not on the treatment but on the patients. They had been bad patients, noncooperative. Even though some of his clientele became sicker, the perception that others improved had demonstrated to the tribe that his remedy could work.

The Fore believed that a sorcerer caused kuru by stealing from his victim a possession, wrapping it with leaves around a stone, casting a spell on it, and burying it in the ground. The stone would start to rattle and, when it did, the victim would begin to shake and get sick. Rocks claimed to be such kuru stones had been dug up and displayed.

After kuru initially broke out, people in hamlets that had all lived in one area now moved away from each other for protection. When deaths continued, the survivors spread even further apart. Still kuru raged. The Fore guarded their belongings more fiercely, to prevent theft. It was then rumored that a sorcerer no longer needed to procure one of his victim's possessions to cause disease, but could make do merely with bits of potato peeling the victim had han-

Robert Klitzman

Residents of a Fore hamlet

dled, or shreds of sugar cane the victim had chewed. Hamlets erected stockades to keep enemies out. Neighboring groups that had once intermarried with the Fore now stopped, fearing the Fore's dangerous sorcery. The Fore were shunned.

"But kuru is caused by a tiny lifelike thing," I explained to Sila and the others now. "Smaller than an insect—a virus. Not sorcery."

"Show it to us," Sila said.

"It is too small to see with your eye and requires a special instrument to view."

"What does it look like?"

"We aren't sure exactly."

"Has anyone ever seen it?"

"It's not clear anyone has."

They all laughed at me. "You white men don't make sense. Kuru is caused by kuru bundles, which we have all seen with our own eyes."

"But you have only heard about the sorcery. There is no proof."

"No. We have seen the kuru bundles ourselves."

"But kuru is decreasing because cannibalism is no longer practiced. The infectious agent has spread through cannabalistic feasts."

"No. Fewer die of the disease because the sorcerers have finally heard our pleas and have seen the evil they have done. Besides, only the older generation knows the poison. The younger generation doesn't possess the knowledge."

"How come anyone dies then?" I asked, thinking I would stump them.

"Because a few old-timers are left here and there who still practice the sorcery," one man answered.

"But small children no longer die of the disease," I said, summarizing the epidemiologic data that colleagues in the past and I had found. "The youngest patients used to be children and are now adults."

"That's because children haven't lived long enough to anger the sorcerers," another man told me. "But others still die. My own brother died of kuru last year."

They all knew people who fell victim each year, and thus they viewed the epidemic in personal, not abstract statistical terms. Even my guides believed in sorcery, though they had worked closely with leading Western scientists, including two Nobel Laureates, D. Carleton Gajdusek, from the National Institutes of Health, and Stanley Prusiner, from the University of California at San Francisco.

My inability to convince the Fore frustrated me. Why couldn't they see that my views were correct? These barefoot villagers, born in a Stone Age society and lacking a written language, were challenging scientific truths and the scientific method itself—achievements considered to rank among the high points and defining accomplishments of Western culture. These New Guineans readily refuted to their satisfaction and dismissed the "universal truths" I had been taught and had accepted. I couldn't disprove the Fore people's arguments without first persuading these villagers that hypochondriacal cases existed, and that my definition and diagnostic criteria for the disease—rather than that of the Fore—were accurate and should be followed.

Yet they had seen and known the disease intimately their entire lives, while I had just landed in their country a few weeks before.

Sila now turned to me. "If you white men think you know what causes kuru," he asked, "why haven't you cured it? We've cured the disease. You haven't!" The natives all believed that Sila's treatment was effective and that his theory was thus correct.

"But discoveries in the West take generations—even hundreds of years," I explained. The group wasn't impressed. The concept of a year had just recently been introduced by missionaries, to mark the arrival of Christmas. Traditionally the Fore lacked a sense of time extending more than a few days forward or backward.

Still the coherence and strength of the Fore's logic impressed me. In fact, years later, as a young doctor, I would also hear arguments similar to Sila's used to explain the successes or failures of treatments in American hospitals. Doctors, too, often blame therapeutic failures on patients' poor compliance or low motivation rather than questioning the efficacy or limitations of the treatments employed.

The year I left New Guinea and returned to the United States, 1981, was the year that the initial cases of AIDS were reported. As the AIDS pandemic spread, I saw how Western reactions resembled Stone Age responses to kuru. Both diseases are fatal. In AIDS, too, fears spread widely. Those infected or suspected of being infected—including gay men and injection drug users—were shunned. For the first 15 years of the epidemic, a desperate search for cures ensued with new advances heralded, often prematurely, and new remedies sought, frequently at considerable expense. Pressures to change culturally sanctioned behaviors that had led to the spread of the disease—sexual and drug use behavior—met with enormous resistance.

Similarly, in the first half of the 1990s, I was surprised to see friends in Great Britain eating beef. In September

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1990, I attended a friend's wedding in Yorkshire, and the next day went to a pub with 12 English friends. Our group ordered 11 portions of roast beef and Yorkshire pudding. I ordered chicken.

"Aren't you afraid of mad cow disease?" I asked my companions, astonished. Five years earlier, in 1985, the first cases of this disease had been found in British cattle. By 1988, hundreds of cows had become ill, and the British government banned giving bone meal feed made from the ground remains of sheep, which can have scrapie, to cattle and other animals as a protein supplement. Still, thousands of cows died. In May 1990, a cat died of the disease. British beef consumption fell, then slowly rose back.

"The beef is now safe," answered Mark, another physician among us, surprised at my question.

"But the virus can take decades before it affects someone," I said. "If even one infected cow gets through, people could become infected and die."

"But the government has experts," Susan argued. "They said the beef's okay." She lifted her fork and bit a piece of pink meat. This willingness to accept government assurances shocked me, given the potential risks.

"I think it's better to be careful," I argued.

"Don't be silly," Susan said. "They have killed all the sick cows. Besides, we grew up eating beef. It's a British tradition."

"But the disease can take 10, maybe 20 years to show up or affect you." They all looked at me like I was crazy.

"It's never been transmitted to man," Mark replied.

"But it's been transmitted to other species," I said.

"That's different. How do you know, anyway? You're an American."

"Yes. But I once studied a similar disease in New Guinea," I said. "Kuru."

It wasn't until three years after this Yorkshire dinner that the first cases of human disease acquired from mad cows were reported. A huge public outcry erupted and almost toppled the British government at the time.

Yet even in that pub, I had seen my friends resisting the notion of these infectious diseases—new, little understood, and having such long incubation periods.

Even in the face of a plague, behaviors involving sex, death, food, and mourning are deeply rooted biologically, imbued with extraordinarily powerful meanings, and hence difficult to change. Individuals seek rationalizations to continue established behaviors: the disease can't happen here; it won't happen to us; results from sorcery and can be reversed by countersorcery; the problem has been solved by government experts; the illness affects only gay men who are promiscuous or don't know their partners.

My experiences with the Fore suggested the need in medicine to examine closely how illnesses and treatments get defined and framed. Diseases aren't givens; they are constructed by cultures in differing ways. I saw how medicine consisted not merely of decision-making trees—as I was taught in medical school—providing definitive solutions to problems, but of events unfolding, shaped by cultural settings and biases. In modern hospitals and clinics, however, these contexts and interpretations usually get ignored.

I have observed closely three major epidemiological outbreaks: kuru, BSE, and AIDS. In all three, people feared the illness but had difficulty understanding it. It was difficult to accept the concept of long incubation periods and equally difficult to change deeply rooted behaviors—eating humans or British beef, having unsafe sex, or using dirty needles. Also, those affected—the Fore, cows, gay men, and injecting drug users—were rejected and shunned. Despite differences in the scientific knowledge base, theories of disease, and cosmological beliefs, basic reactions to these diseases resembled each other. In the absence of clear, visible evidence of infection, disbelief and pseudoscience persisted.

Belatedly, the lessons of these diseases have begun to sink in. Many individuals at risk for HIV have begun changing their behaviors. Still thousands of new cases of infection still occur every year. The British government eventually slaughtered millions of cows.

Over upcoming years, other epidemics will arise, as technology alters environments and human lives, linking formerly isolated regions of the world such that infectious agents harbored in one ecosystem can escape to others. New plagues will no doubt prompt fear, resistance, and denial, furthering the spread of disease, and inspiring desperate searches for answers and solutions, such as I saw in New Guinea.

New Guineans dismissed my views and I could dismiss theirs. But similarities remain.

Robert Klitzman is the author of A Year-Long Night: Tales of a Medical Internship (Viking Press; 1989), In a House of Dreams and Glass: Becoming a Psychiatrist (Simon and Schuster; 1995), Being Positive: the Lives of Men and Women with HIV (Ivan R. Dee, Inc.; 1997), and The Trembling Mountain: a Personal Account of Kuru, Cannibals, and Mad Cow Disease (Plenum; 1998).

News and Features

Haunting cases: a teenager with Hodgkin's who shunned conventional therapy

Sarah Scott, Toronto, Ontario, Canada see also p.150

When doctors told Derek Poulin that he would need chemotherapy and radiation to save his life, the 15-year-old was adamant. He would not do it. It was the spring of 1998 and Derek had just been told that he had Hodgkin's disease. Doctors assured him that with radiation and chemotherapy, he would have an 80% chance of survival. But Poulin, a 10th-grade student in Calgary, Alberta, saw the children with cancer in the Alberta Children's Hospital and became scared. He witnessed the side effects—the nausea, the hair loss, the possibility of secondary cancers. "I thought I'd be throwing away the rest of my life."

Poulin decided on an alternative strategy, suggested by his grandfather, Ron Poulin—a new pill based on cow colostrum. His mother, Joanne Poulin, agreed. The maker of this potion, a company based in Quebec, claims that it can boost the body's immune system and kill off cancer cells. Oncologists say there is no basis for this claim.

The case threw doctors at the hospital into a quandary. The teenager and his family could not be dissuaded from their decision to opt for an unproven alternative therapy. His physicians decided not to attempt to seek a court order compelling Poulin to have conventional therapy, but they urged him to keep visiting the hospital clinic while he was taking the cow colostrum.

Four months later, Poulin was suffering night sweats. "The doctor told me if I didn't do something, I'd be dead in two months," he says. He finally agreed to chemotherapy and radiotherapy. Poulin's prognosis is good, his doctors say, but because of the delay, he needs more intense therapy over a longer period of time, which exposes him to a higher risk of heart or lung problems as well as secondary cancers caused by the therapy.

The case still haunts Dr. Max Coppes, a pediatric oncologist at Alberta Children's Hospital. He is concerned that the phenomenal popularity of alternative medicine is inducing families to shun proven conventional therapy, choosing unproven alternatives instead. Children now have over a 70% chance of surviving leukemia, compared with a 5% chance in the 1960s. The prognosis for children with Hodgkin's disease is excellent. Instead of talking about survival, says Coppes, "We're talking about getting on with life."

Yet some parents, desperate to help their sick children, are opting for the unproven "cures." "You can never blame parents for making that decision at that time," says Dr. Coppes. The days after a child is diagnosed with cancer are pitch-black, he says. "You don't see anything. You don't hear anything." He knows: he and his wife have suffered the death of one of their children. He can understand the temptation of unproven remedies that offer a sliver of hope—and without the sickness that accompanies the conventional therapy. "These are absolutely desperate people, a very vulnerable population," Dr. Coppes says. But he believes doctors have a duty to warn patients about the potential dangers of unproven cancer remedies. "We have an obligation to protect vulnerable parents in the phase where they have just heard their child has cancer. We have to protect them from harming themselves and from being harmed by others," he says.

> "To believe you can take colostrum from cows to kill cancer is absolutely ludicrous."

The pills that Poulin took are called Matol Biomune OSF Plus. Matol has been advertising the alleged benefits of this "dietary supplement for immune system support" on its Web site, in literature it hands out, and on the company's information line. The potion contains extracts of colostrum from a "select herd of cows raised in strict organic conditions," along with astragalus, "a traditional Chinese herb known to stimulate immune response." The theory, according to the company, is that the substance will boost the body's immune system by increasing the activity of natural killer cells "whose mission is to seek and destroy any harmful invaders that penetrate the body's initial defense positions." The company even offers a 30-day money-back guarantee.

Dr. Sheila Weitzman at Toronto's Hospital for Sick Children voices the feelings of many oncologists: "To believe you can take colostrum from cows to kill cancer is absolutely ludicrous." But scientific skepticism doesn't bother the makers of Matol, based in Lachine, Quebec. "I believe it is helpful," Matol chairman J.F. Robert Bolduc says. "Any product that enhances and supports the immune system is going to be helpful. But is it a cure? Absolutely not. It doesn't claim to be."

In some cases, Canadian courts have allowed doctors to impose a life-saving therapy even if parents want to deny it to their children. While parents can choose to shun treatment for themselves, the courts have said, they cannot deny it to a young child, who is seen as unable to choose. But in order to take the legal route, doctors have to prove that the therapy offers a good chance of survival. The child also has to be too young to make an informed decision. Canadian courts have ruled both ways, depending on the child's age, the sickness, and the remedy proposed by doctors.

Because Derek Poulin was 15, Coppes decided to forgo the legal route. "This is a teenager," says Dr. Coppes. "How can you force a teenager?" He also wanted to keep the door open for the boy and his family to return to the hospital if they changed their minds.

Poulin's mother, Joanne, remembers the heavy pressure from doctors to make her son take conventional therapy. "They told me I was killing my son, that I was signing his death warrant," she says. Frightened by being ill, Derek Poulin didn't continue taking the Matol—instead, he ran away from home. He was getting increasingly ill until finally his mother coaxed him home, in August, telling him that he would be dead by Christmas without chemotherapy. Despite the success of the chemotherapy, Poulin and his mother still believe the Matol product might have helped.

"We never had an opportunity to give it a chance," says Joanne Poulin. "I still believe in my heart that we could have put it into remission.

"I've watched Derek waste away for the last four months [on chemotherapy]. He throws up every day. He has no hair. He's lost 30 pounds. The cure is almost evil. It's barbaric. There's got to be a better way."

If there is a better way, says Dr. Coppes, it should first be properly tested to see if it works and if it is safe.

Father sues doctor over right to be told of alternative therapy for child's brain tumor

Sarah Scott, Toronto, Ontario, Canada

Are you obliged to tell your patients about an alternative remedy—even if it's unproven, and most physicians are skeptical about the inventor's claims of incredible success?

These are the core questions in a lawsuit against Dr. Michael Prados, a neuro-oncologist at the University of California at San Francisco. Dr. Prados is being sued by the family of a little girl who died at the age of six in 1995.

In January 1993, Chrystin Schiff was diagnosed with a rare, highly malignant brain tumor. Neurosurgeons at UCSF's medical center removed most of the tumor, and she received chemotherapy and radiation. By June, conventional therapy was completed and most of the tumor was gone.

AP Photo/Pat Sullivan

Dr. Burzynski with supporters

Many oncologists have for years expressed deep skepticism about Dr. Burzynski and his astounding claims of success

In August, Chrystin and her family traveled to Houston, Texas, to visit Stanislaw Burzynski, a doctor who has made controversial claims to have discovered a remedy with astounding results, even for highly malignant brain tumors. The remedy consists of antineoplastins, a substance that was originally extracted from urine but is now made synthetically.

Chrystin started taking antineoplastins, and the rest of the tumor seemed to fade away. But in the summer of 1994, Chrystin developed other problems—a brain hemorrhage, loss of vision, and difficulty walking. By the spring of 1995, Chrystin had become blind and had lost her ability to speak and to walk. She died on 29 July 1995 "of aspiration pneumonia," according to the autopsy report. "No evidence of residual/recurrent malignant tumor was identified, but an extensive leukoencephalopathy probably related to a combination of radiation and chemotherapy effect was present," the autopsy report said.

Ric Schiff, Chrystin's father, is convinced that her cancer was cured by antineoplastins. He states, "the ultimate cause of death was brain damage as a result of radiation and chemotherapy."

Although Dr. Prados was not Chrystin's doctor, as head of neuro-oncology he sat on the hospital's tumor board when Chrystin's case was discussed. After Chrystin's chemotherapy and radiation treatment was completed, he met with the Schiffs to discuss Dr. Burzynski's treatment. According to Ric Schiff, Dr. Prados discouraged the family from using Dr. Burzynski's remedy.

In fact, many oncologists have for years expressed deep skepticism about Dr. Burzynski and his astounding claims of success for treating brain cancer. Dr. Burzynski reports, for instance, that he tested antineoplastins on 12 patients with brain tumors for a median 232 days. Of the nine patients who were evaluated in the study, five reported a "partial response" (their brain tumors shrank) and another three were "stable." In one patient, the tumor grew. Although Burzynski claims to have published hundreds of studies, oncologists are not impressed with their scientific quality. None of his research papers has been submitted to a peer-reviewed journal.

Before the Schiff case, Dr. Burzynski had been engaged in a long and heated battle with the Food and Drug Administration. For years the FDA had been trying to get Dr. Burzynski to submit his antineoplastins to rigorous tests to determine whether it was an effective treatment for cancer. In 1983 Burzynski's refusal led a US District Court judge to issue an order to stop him from sending drugs across the state borders without a license from the FDA to investigate a new drug. That injunction became permanent in 1984. Two years later, an FDA investigation indicated that Dr. Burzynski was still shipping his antineoplastins across the Texas border. The case was referred to the US Department of Justice in June 1985. Dr. Burzynski filed a counterclaim, alleging FDA misconduct.

Despite these legal maneuvers, the US government had not given up on the diplomatic approach. In 1991, investigators from the National Cancer Institute (NCI) visited Dr. Burzynski to look at his best results. They could not see, however, whether the patients in the studies had any prior treatment that might explain a positive result. NCI investigators said further investigation was warranted and sponsored a trial of brain tumor patients. That trial ended in 1995 amid much acrimony and with no definitive conclusion.

In 1993, when he met the Schiffs, Dr. Prados knew about Dr. Burzynski's unorthodox treatment—at least one of his patients

had taken antineoplastins. That knowledge is why he is now being targeted by the Schiffs. "He's the only one who knew specifically about Dr. Burzynski's medicine," says Ric Schiff. "If UCSF knew or should have known that there was a potential treatment that cured brain tumors with no long-term side effects, why didn't they tell us when we asked if there was any other possible treatment?"

California law is not clear on what doctors must disclose to their patients. A 1972 judgment from the California Supreme Court lays down a general rule: "There is a duty of reasonable disclosure of available choices with respect to proposed therapy and of the dangers inherently and potentially involved in each." Some judges have interpreted this to mean that doctors do not have to disclose a treatment that, in their opinion, does not help the patient.

The judge trying the case ruled on narrower legal grounds. California law forbids doctors from authorizing treatment unless the federal government or the state of California has approved the drug or has granted permission to investigate it. As the hospital doctors pointed out, Dr. Burzynski did not have government approval to ship antineoplastins across state lines in the summer of 1993 when Chrystin started treatment.

Last February, Judge David Garcia of the California Superior Court agreed with the hospital's lawyers and dismissed the case against Dr. Prados. The Schiffs are appealing. The family is also suing the hospital for giving their daughter a lethal dose of chemotherapy and radiation without obtaining the proper consent.

The court ruled on a technical argument about the legality of the treatment back in 1993. But were Prados and fellow doctors under an obligation to tell the Schiffs about an unorthodox, unproven treatment? Dr. W. Byron Smith, the oncologist who treated Chrystin, thinks not. He sympathizes with the Schiff family but says that Burzynski had never held a proper clinical trial to prove that his remedy worked. He still hasn't.

Smith also thinks that UCSF handled Chrystin's case very well and that it was appropriate to give chemotherapy and radiotherapy after some of the tumor persisted after surgery. And what if Chrystin had gone on antineoplastins instead of going through chemotherapy and radiation? "She would have died within 3 to 6 months," Smith believes. "But without a clinical study, no one knows."

US agency to test safety of four herbs

Scott Gottlieb, New York

Four popular herbal supplements are to undergo safety checks, the US National Toxicology Program has announced. The program, a coalition of agencies that includes the Food and Drug Administration, the National Institutes of Health, and the Centers for Disease Control and Prevention, will test aloe vera, ginseng, kava, and milk thistle. Researchers are expected to look at whether the substances are carcinogenic.

The substances were originally nominated for testing by the National Cancer Institute. The recommendations were then reviewed and approved by the federal Interagency Committee for Chemical Evaluation and Coordination, which advises the National Toxicology Program. No data indicating a problem are required for nomination to the program. More than 30 substances are tested by the program each year through rodent and in vitro studies, said Dr. William Easton of the National Institute of Environmental Health Sciences. No humans are tested.

One of the most widely used products among those chosen for testing, aloe vera, is commonly used to soothe burned skin, but it is increasingly turning up as a beverage, with claims that it can fight disease by "cleansing" the digestive tract. Dr. Easton said that researchers have noted some similarities between aloe vera and croton oil, a known carcinogen. Other substances that have been nominated for testing are kava, which is popularly believed to work as a muscle relaxant and mood enhancer; ginseng, which is touted as an energy booster; and milk thistle, which is thought to have anticancer properties and to improve liver function.

A fifth substance nominated for testing, indole-3-carbinol, is found in cruciferous vegetables (a family of plants with cross-shaped flowers, such as cabbage and turnip). Indole-3-carbinol is believed to have potential to reduce the risk of cancer.

News in brief

Rise in number of mentally ill in US prisons

A growing number of people with mental illness are being held in US prisons, claims the Department of Justice's first in-depth national study of mental illness in prisons. It reports a total of 283,800 prison inmates with some form of mental illness in mid-1998. That number represents about 16% of the total prison population, compared to a previous literature review that suggested 6% to 15% of people in city and county jails and 10% to 15% of inmates in state prisons had severe mental illness.

The more recent report blames the wave of deinstitutionalization that started in the 1960s. The number of people in state psychiatric hospitals decreased from 559,000 in 1955 (out of a population of 165 million) to 72,000 by 1998 (out of a total national population of around 250 million). The Department of Justice study found that mentally ill people in state prisons were twice as likely as other prisoners to have been homeless before their arrest and to have been physically or sexually abused in childhood. The study has been criticized because it relied on answers given by prison inmates themselves. A copy of the study, Mental Health and Treatment of Inmates and Probationers, is available on the Internet at www.ojp.usdoj.gov/bjs/pub/.

FDA halts urokinase sales

The US Food and Drug Administration has stopped shipments of urokinase after fears that the drug could be contaminated by mycoplasma. This action follows accusations that constituents of the drug were manufactured by using kidney cells from aborted fetuses obtained without proper consent from the mothers.

British Columbia first province to license acupuncturists

see also p.149

British Columbia has become the first Canadian province to regulate and license acupuncturists. All acupuncturists in the province will be required to obtain approval from a new organization, the College of Traditional Chinese Medicine and Acupuncture Practitioners of British Columbia. Establishment of the College is being billed by provincial officials as the first step toward health-plan coverage of Chinese medicine by the province, which pays for most treatments offered by conventional physicians in British Columbia. A physician speaking for the British Columbia Medical Association was quoted in the Canadian newspaper, The Globe and Mail, as being concerned that the new regulatory body included no researchers or academic physicians, only "true believers" in acupuncture.

West of the Rockies

Speaker's Corner

Becoming an integrated physician: first step is acupuncture training

Last year I set out to pursue acupuncture training. My experiences studying acupuncture and my early results using acupuncture to treat myself and my patients have changed my professional outlook.

I have been aware of acupuncture for many years. On trips to visit family in China in the 1970s and 1980s, I had a chance to observe some acupuncture practices. My curiosity was piqued, and I read a few books.[1,2] In 1985 I learned a few acupressure points from a nursing colleague and used them in my clinical work to treat tension headaches, neck pain, and upper back muscle tension, with good results. In 1997 two developments helped me commit to learning acupuncture. First, the National Institutes of Health came out with its Consensus Guidelines on Acupuncture,[3] which made it easier to find acceptance for acupuncture as a worthy option for clinical practice. Second, I received a series of intermittent acupuncture treatments from a Chinese acupuncturist (and friend) in Los Angeles to treat a persistently stiff and swollen sprained ankle that had not responded to ibuprofen and physical therapy. Over several weeks I received four to five treatments. The swelling improved with each treatment and finally resolved.

When I looked for acupuncture training opportunities in the summer of 1998, there seemed to be several options:

(1) short courses (half a day to one week, $150 to $400)
(2) longer courses (six months to a year), such as the UCLA course in Medical Acupuncture for Physicians, the USC course in Chinese Acupuncture for Physicians, and the North American Symposium on Acupuncture (about $5000)
(3) an even longer course (two to three years) with a traditional Chinese medicine school-based training program (about $20,000).

For me, a year-long course presented the most feasible option, and I registered for the UCLA course. The course offered two tracks, one for primary care physicians and the other for physicians specializing in pain management. Both tracks featured the same text and 35 core videotapes. Primary care physicians reviewed another 20 videotapes and pain specialists viewed another 12 videotapes.

We learned how to insert acupuncture needles first into ourselves and then into other physicians who had enrolled.

After being accepted for the course, I received the text and three videotapes demonstrating the location of acupuncture points. Two months later I attended the inaugural four-and-a-half-day conference, which consisted of lectures on acupuncture points and workshops teaching anatomy and palpation of the musculoskeletal system. We began to appreciate that acupuncture meridians followed natural contours along muscle edges and that points often were found in natural subtle depressions. We received guided instruction on kinesthetic senses, aimed at helping us learn to decipher and understand the nonverbal but palpable history of a person's body. We learned how to insert acupuncture needles first into ourselves and then into other physicians who had enrolled. The needles are fine-gauge (32 g or smaller), solid, and flexible. On the second day of the course, I felt comfortable enough to give myself my first acupuncture treatment for a calf muscle cramp. The 20-minute treatment was relaxing, and it relieved the spasm.

After returning home I received 55 videotapes in the mail. A large portion of the core tapes demonstrated each acupuncture point along the 12 principal meridians. Point localization is essential, of course. Watching the

tapes was instructive but tortuous. It evoked in me the same tepid zest as watching a video of a dictionary from cover to cover would have. Most of the material was covered in written texts, and I was able to assimilate by reading much faster than by watching tapes. Overall, the course provided me with a good foundation of acupuncture, and I would highly recommend it.

I recently joined the integrated Chinese-Western medicine practice of another family physician. Even when working in my previous practice, I had discussed my patients with my future partner two or three times a week, enjoying a long-distance preceptorship. In the first 6 months of 1999, I treated 33 patients with acupuncture, 15 women and 18 men ranging in age from 17 to 76 years. Most patients appeared to improve when seen in follow-up.

For me, there are several positives about practicing acupuncture. Now that I am able to evaluate patients under two different paradigms, some patients who had long lists of multiple problems appear to have cohesive patterns under a traditional Chinese framework. I have a renewed sense of optimism that I can actually do more for my patients now. Most patients enjoy their acupuncture treatments, feel more relaxed, and have good results. It is great to lay hands on patients who usually go away feeling better already. I find it more intellectually satisfying to think through the acupuncture approachs and the specific points that will best suit a particular individual instead of doing maintenance prescription medication checks.

Some patient outcomes have been dramatic, forcing me to discard my previous expectation of limited prognosis based on Western allopathic medicine alone. I once watched my partner treat a new patient who presented with a frozen shoulder. With moxibustion (applying a heated herbal cigar) to one leg acupuncture point and then to the patient's shoulder and hand, the problem resolved. As a midlife clinician, I find it wonderful to discover new clinical tools that can make a difference in patients' lives. Instead of sharing my satisfaction over improved patient outcomes, however, some of my colleagues have been skeptical, wanting evidence that the treatments really do work and are not a placebo response.

AP Photo/Natasha Lane

Acupuncture points are found on the face

This skepticism is one of the challenges that accompanies learning acupuncture. Another challenge is gaining sufficient skill and experience to feel self-confident. I accomplished this by having an experienced acupuncturist as my preceptor, but I question how feasible that strategy would be for many of the physicians taking acupuncture courses. It also takes more time for me to do acupuncture treatments, so I am less productive in terms of the number of patients seen in a day. I wonder, though, what do productivity numbers mean when patients' health problems are not resolved?

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Houston, TX 77098

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3 National Institutes of Health. Acupuncture. Consensus Development Statement, 1997. Available from: URL:http://odp.od.nih.gov/consensus/cons/107/107_statement.htm

Resources

Helms Medical Institute, 2520 Milvia Street, Berkeley, CA 94704. Tel (510) 649-8488; fax (510) 649-8692; www.helmsmed.com
The goal of the institute is to further the training and standardization of practicing physicians to serve as acupuncture preceptors in the UCLA course.

Christina Stemmler, MD, and Lawrence Li, MD, MPH; The Center for Integrated Medicine, 3120 Southwest Freeway, Suite 415, Houston, TX 77098. Tel (713) 523-4181; Fax: (713) 523-4184; www.integratedmedicine.com

capsule

Chest exams are not reliable Examining the chest is second nature to most physicians even though it is not a reliable diagnostic maneuver (Archives of Internal Medicine 1999;159:1082-1087). Clinical exam alone has a sensitivity of about 50 percent for picking up pneumonia and a specificity between 60 and 70 percent according to the study from Seattle. The most useful bits of the exam were listening to breath sounds with the patient upright or lying on one side.

capsule

More milk please Girls in their teens who drink plenty of milk may end up with higher peak bone mass as adults, say investigators who asked over 224 women about their childhood and teen calcium intake (American Journal of Clinical Nutrition 1999;68:1014-1017). The findings, although observational, support other work showing that giving calcium supplements to teens can increase their peak bone mass. Unfortunately many teens prefer diet coke.

Letter from the Southwest

Steamrolling the tentorium

Mark Carroll, Flagstaff, AZ, mcarroll@infomagic.com

Imagine making an appointment to see your doctor. "I'm having strange dreams," you tell him. "Last night, for example, I dreamed I was lying on a potholed road that was being resurfaced. One machine was pouring new pavement. Another—a steamroller—was flattening it, compacting it. I noticed the steamroller heading toward me. When I tried to get out of the way, to stand, to move, I suddenly realized I WAS THE PAVEMENT, I was part of the new surface. I screamed for the steamroller to stop but no one listened. No one was at the wheel.

Your doctor looks at you. He steeples his fingers, asks about physical symptoms. You have none. Your doctor briefly examines you, then pronounces you fit. "Try not to worry so much," he says. He moves toward the door, but you stop him. "This means something," you say. His hand rests on the doorknob. "What did you have for dinner last night? Studies have shown that eating too close to bedtime can cause unusual dreams." He smiles and quietly leaves.

This scenario is obviously exaggerated: most of us know better than to see our doctors about disturbing dreams. Instead, we ignore our dreams, forget them, laugh at them occasionally over coffee with friends. Sometimes, if the dreams recur, we browse bookstores and read chapters on the psychology of dream symbolism while pretending to consider buying books on child development or home repair. We want to know more about our dreams, about (dare I say it) our *unconscious selves*, yet are afraid that focusing too much on dreams might somehow validate bizarre parts of our psyches that should best not be considered. Conscious life is a tricky enough business without overturning the smouldering ashes of our buried fears, our hidden aspirations.

How can medicine study dreams? How can a doctor diagnose images that burn patients' visions during sleep but are inapparent when they disrobe to be examined?

There are people who specialize in dreams. The medical profession knows them as psychologists, Jungian analysts, spiritualists, "New Age" healers. Sometimes, if a patient is persistent, seems especially pained, or acts potentially litiginous, primary care doctors refer to such "specialists." We flick our eyebrows at colleagues, softly describe the problem as "supratentorial," then move on, hoping that the next patient will present something more tangible, and consistent with our one cause-one effect view of the world.

> Why have we spent so much time studying strep throat and coronary artery disease yet so little learning about maladaptive emotions, unarticulated intentions, and recurrent dreams?

None of us likes this pigeonholing. We would prefer to be the openminded healers that patients want, yet somehow we get stuck in patterns of listening and interacting that leave both us and our patients feeling inadequate and cheated. Collectively we turn to integrative health as a beacon of practical possibility. We'll bring the best of all traditions together, we say. We'll study herbs, homeopathy, and biofeedback in the same way we study new drugs: rigorously, scientifically. We'll learn to use whatever works.

But some types of integration differ little from what we already have. Herbs, homeopathic remedies, and biofeedback techniques may expand our options for treatment; they will not necessarily change our approaches to diagnosis, will not force critical reconsideration of how we listen, how we apportion limited resources, how we segregate symptom and sign into categories above or below the arbitrary line of "tentorium." How might latent disease be manifest in current demeanor and dreams? We do not know. How might demeanor and dreams be subtle attempts at psychological healing or evidence of illness which, if unheeded, may later manifest as organ system dysfunction and disease? We seem embarrassed to ask.

The abyss dividing mind and body cannot be spanned by simply redefining what types of salves, salts, and solutions qualify as statistically effective. Somehow medicine must reevaluate its biases and limitations. Why have we spent so much time studying strep throat and coronary artery disease yet so little learning about maladaptive emotions, unarticulated intentions, and recurrent dreams? Why do we lecture so much about physiological risk factors for disease yet so little about psychological ones?

Newer tests for strep throat and cardiovascular disease fit quite neatly into the socioeconomics of modern medicine. Newer approaches to mind do not. Yet if more of us speak up, maybe the dialogue on health can incorporate "supratentorial" possibilities instead of dismissing them. After all, as medicine smooths itself with a shinier, more integrated surface, all of us will become part of the new pavement. Wouldn't it be nice to influence the direction of the steamroller before it indifferently presses us into service?

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NOVEMBER 5-7, 1999: **11th Annual Anesthesiology Update.** Monterey Plaza, Monterey, CA. Contact (916) 734-5390.

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CARDIOLOGY

OCTOBER 30, 1999: **Update in Electrocardiography and Arrhythmia.** UCSF at Radisson Miyako Hotel, San Francisco, CA. 7.5 hrs Cat. 1. $195. Contact: UCSF Department of Medicine, CME, UCSF Box -0656, San Francisco, CA 94943-0656. (415) 476-5208.

DECEMBER 17-19, 1999: **Advances in Heart Disease.** American College of Cardiology at Grand Hyatt Hotel, San Francisco, CA. 16 hrs Cat 1. $490-565. Contact: ACC, Attn: EP, P.O. Box 7931, Baltimore, MD 21279-0231. (800) 253-4636, ext. 695.

DECEMBER 17-19, 1999: **The 16th Advances in Heart Disease.** San Francisco on Union Square, San Francisco, CA. 16 hrs Cat. 1. Contact: Registration Secretary, Extramural Programs Dept., 9111Old Georgetown Rd., Bethesda, MD 20814-1699; (800) 253-4636, ext. 695.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

OCTOBER 15-17, 1999: **Complementary and Alternative Medicine: Practical Applications and Evaluation.** Stanford Center for Research in Disease Prevention and Center for Alternative Medicine Research and Education, Beth Israel Deaconess Medical Center at Sheraton Palace Hotel, San Francisco. 18 hrs Cat. 1. Contact: Professional Meeting Planners, 5 Central Square, Suite 201, Stoneham, MA 02180; (781) 279-9887; kbates@pmpmeeting.com.

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OCTOBER 25-29, 1999: **Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco, CA. 32 hrs Cat 1. $675. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656. (415) 476-5208.

OCTOBER 28-31, 1999: **California Board Review. A Comprehensive Review of Emergency Medicine.** American College of Emergency Physicians at Paradise Point Resort, San Diego, CA. 50 hrs. $895. Contact: EMEDS at (888) 616-1711.

ENDOCRINOLOGY

OCTOBER 22-24, 1999: **Clinical Endocrinology for Primary Care Physicians.** Tropicana, Las Vegas, NV. CME 11 hrs Category I. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; (800) 421-3756, Fax (303)798-5731.

FAMILY PRACTICE/PRIMARY CARE

OCTOBER 22-24, 1999: **Clinical Endocrinology for Primary Care Physicians.** Medical Education Resources at the Tropicana Hotel in Las Vegas, NV. 11 hours. Contact: MER Linda Main, Meeting Coordinator, 1500 West Canal Ct., Ste. 500, Littleton, CO 80120-4569; (800) 421-3756.

OCTOBER 28-31, 1999: **11th Annual CME/Golf Meeting.** Nevada Academy of Family Physicians at The Orleans Hotel & Casino, Las Vegas, NV. Contact: Barbara Bolling, NAFP, P.O. Box 27713, Las Vegas, NV 89126-1713. (702) 228-5852; e-mail to:nafplvbb@aol.com.

DECEMBER 2-3, 1999: **Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco, CA. 13 hrs Cat 1. $370. Contact: UCSF Department of Medicine, CME. UCSF Box 0656, San Francisco, CA 94143-0656. (415) 476-5208.

DECEMBER 10-12, 1999: **Issues in Women's Health.** Medical Education Resources at Tropicana Hotel, Las Vegas, NV. 11 hrs Cat 1. Contact: Linda Main, Meetings Coordinator, MER, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569; (800) 421-3756, Fax (303)798-5731.

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GENERAL/MULTIDISCIPLINARY

OCTOBER 21-22, 1999: **8th Symposium on Clinical Trials: Design, Methods and Controversies.** UCSF Laurel Heights Campus, San Francisco. 12 hrs Category I. $325 for physicians; $325 for nurses and allied health professionals; $150 for physicians in training. Contact: Registration office at (415) 502-1795.

OCTOBER 22, 1999: **Aesthetic Facial Surgery: The Evolution of Oculoplastics.** Renaissance Orlando Hotel, Orlando, FL. 6.75 hrs Cat 1. $400-450. Contact: Amy Wood, The Professional Image, Inc. (949) 760-1522.

GENERAL

OCTOBER 1-4, 1999: **Converse in Spanish.** Maricopa Health System at Scripps Memorial, San Diego; November 12-15, 1999Glendale Adventist Medical Center 36 hrs. $695. Contact: Rios Associates (619) 218-4875

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To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850. Brochures, course information, and registration forms are available from the contact person or organization.

TUESDAY NOON CONFERENCES: **Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

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CONTACT INFORMATION
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PCMS CME: Contact:Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.
U/W (UNIVERSITY OF WASHINGTON): Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA98195. (206) 543-1050.
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Health practices and culture

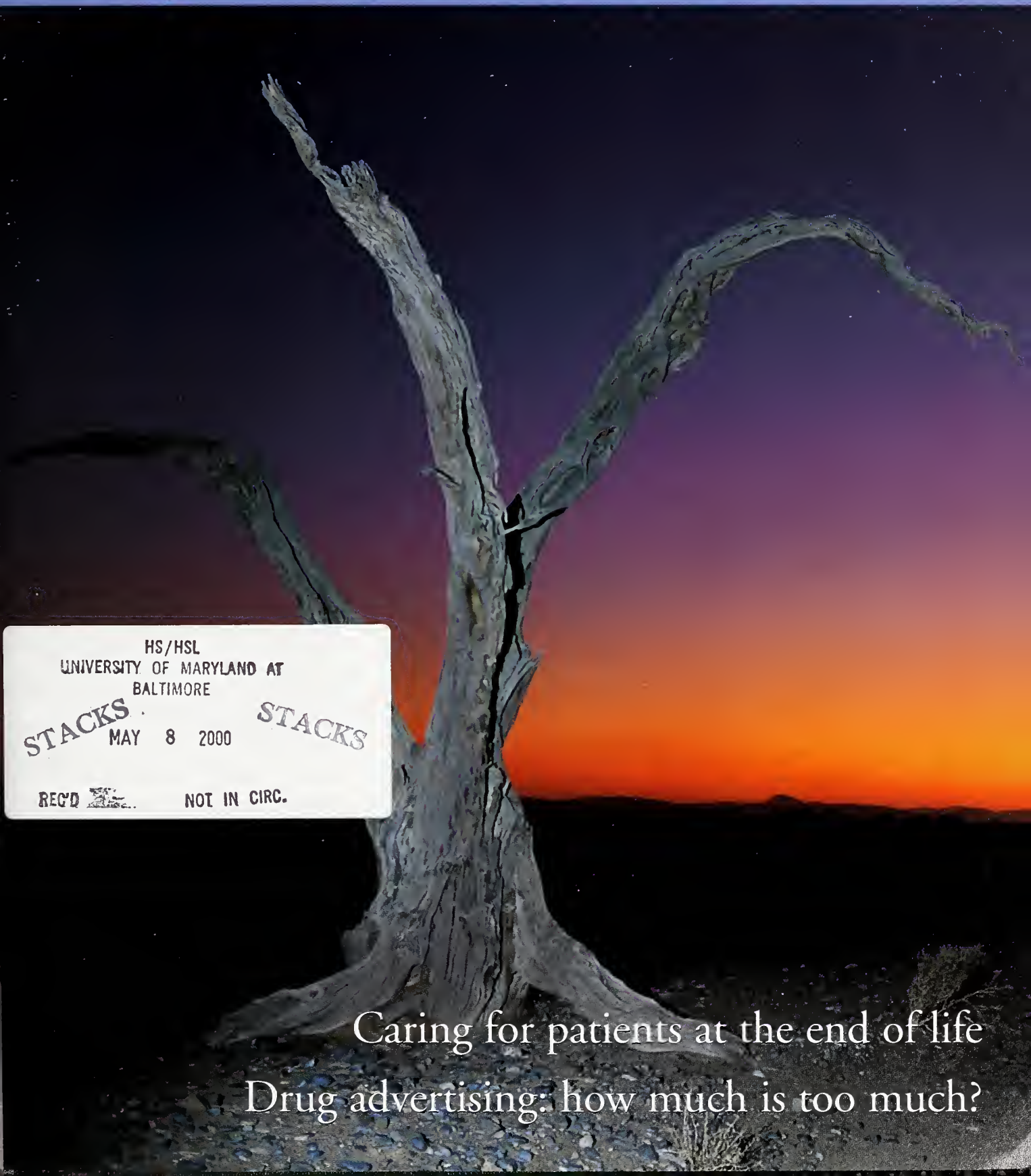
David Heiden

Because her baby was less than 40 days old, this mother carried a dagger to keep away evil spirits. Somalia, 1982.

David Heiden is an ophthalmologist practicing in San Francisco.

wjm

western journal of medicine Volume 171 Number 4 October 1999



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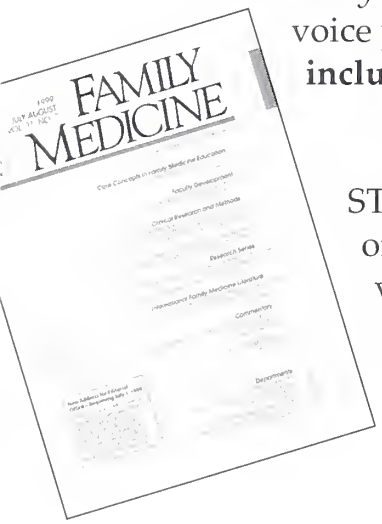

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Editor's pick

Two years ago this month, a law permitting physician-assisted suicide went into effect in Oregon. This issue of WJM marks that anniversary by focusing, in part, on death. In his Speaker's Corner (p.279), Peter Goodwin, who has been intimately involved with the Oregon experience, describes his efforts to help a family. The language Goodwin uses with this family is unusual, and some may find it disturbing. But, as Joanne Lynn reminds us in her commentary on Goodwin's article (p.281), this is territory in which the language remains unsettled.

Whatever their views of assisted suicide, most people would agree that we could do a better job of caring for people who are dying. Several of the articles in this issue of WJM aim toward that goal. Pantilat tells us how to relieve pain more effectively (p.257) and suggests that we could offer more substantial support at the end of life (p.253). Rabow and McPhee provide concrete examples of how we might communicate more effectively. Hallenbeck and colleagues explore the issue of terminal sedation and provide a rationale for its use. Milch (p.224) writes that for people to be able to die where they want to, federal reimbursement policies may need to be revamped.

While Oregon's experience of physician-assisted suicide is raw and new, doctors in the Netherlands have been providing this service, along with euthanasia, for far longer (p.268). A series of court cases from 1969 to the 1990s established the criteria that physicians must follow before carrying out these practices. Physician-assisted suicide is still illegal, but physicians are not prosecuted if they satisfy six requirements; the request must be voluntary, well considered, and lasting; the suffering must be unbearable with no alternatives for relief; and physicians must consult a colleague and keep a written record. Physician-assisted suicide is always done at home and is a sixth as common as euthanasia. Whereas in Oregon the doctor does not have to be there when the patient takes the lethal dose of medication, in the Netherlands, the doctor must be there.

One of the arguments against physician-assisted suicide is that it is the start of a slippery slope. Many physicians will feel uncomfortable reading Tony Sheldon's news report from Utrecht in the Netherlands (p.275) on a doctor who escaped prosecution after helping an elderly patient with dementia to die. The Alzheimer's Foundation in the Netherlands has condemned it forcefully, saying that patients with dementia cannot provide informed consent.

Unease over possible abuses of the right to die may be reflected in bills to legalize physician-assisted suicide floundering in about 28 states over the past 2 years, including Arizona, California, New Hampshire, and New York (p.274). Three states, Michigan, South Carolina, and Virginia, have even passed new bans on the practice. There is, however, some evidence that just raising the issue of physician-assisted suicide, may improve the health care of terminally ill patients. When Rhode Island implemented a new ban on assisted suicide in 1996, there were fears that physicians would restrain their morphine use. In the following year, however, morphine use for pain relief in the region more than doubled.

Also in this issue, Glassman et al. (p.234) explore the growing problem of conflicts of interest—in particular, whether pharmaceutical promotions in medical journals create conflicts of interest for owners that are nonprofit medical organizations. Not surprisingly, the authors found that many organizations rely to a great extent on income from pharmaceutical companies to support their journals and in turn their parent organizations. The authors speculate on the effect this reliance may have on the journal's motivation to provide readers with accurate and truthful information. In an accompanying commentary, Lexchin (p.238) further explores the link between drug promotion and conflicts of interest involving the practice of medicine.

—Michael S. Wilkes
—Miriam Shuchman

Visions of the dead and near-dead hold a power all their own—
WJM is pleased to include in this issue photographs from an exhibit titled Hospice: A Photographic Inquiry. Organized by the Corcoran Gallery of Art and the National Hospice Foundation, this exhibit explores the experience of hospice care through the eyes of several internationally recognized photographers. The works of two of these artists—Nan Goldin and Jack Radcliffe—grace the pages of this issue. In 1999 and into 2000, the exhibit, accompanied by a published catalog, will travel to Houston, TX, Charlotte, NC, Minneapolis, MN, and Salt Lake City, UT.

Jack Radcliffe

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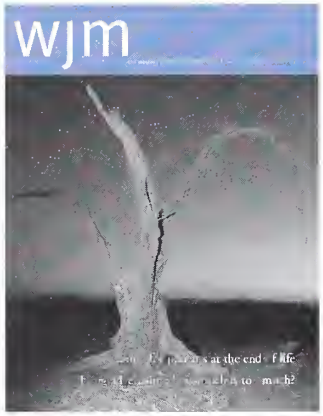

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Op-Ed

Storm warnings over Oregon

Wesley J. Smith
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Before physician-assisted suicide was legalized by initiative in Oregon, advocates of the measure assured voters that it would be limited strictly to those rare cases in which patients were in "severe, unrelenting, and intolerable suffering" that could not be otherwise relieved.[1] This impression was bolstered during the campaign via a television advertisement in which an Oregon nurse admitted to assisting her daughter's suicide because the young woman was in severe untreatable pain from bone cancer. Oregon voters were also told that legalized suicide would be carefully monitored through strict legal guidelines and that hastened deaths would take place "in the context of a meaningful doctor-patient relationship" and then only after a deep and thorough discussion of all options between trusting patients and devoted physicians.[2]

That is not how assisted suicide has actually worked. An analysis of the first reported legal assisted suicide, of a woman with terminal breast cancer, based on information released by the assisted suicide advocacy group Compassion in Dying (CID), disclosed that the woman did not commit assisted suicide because of unbearable suffering and agony. Rather—in her own words, played on audiotape posthumously at a CID news conference—she wanted to "be relieved of all the stress I have." But stress caused by dying and growing debilitation, while certainly a very real and substantive medical issue, is a treatable condition that does not require killing to alleviate.

A subsequent in-depth analysis of this case by three medical and bioethics experts revealed an even more detailed account of these troubling events. Upon receiving her terminal diagnosis, the woman asked her treating doctor to assist in her suicide. The doctor refused. She consulted with a second doctor, who also declined and diagnosed her as depressed. She then contacted CID, whose medical director, Dr. Peter Goodwin, spoke with her twice on the telephone, after which he decided that she wasn't depressed but merely "frustrated." Goodwin then referred her to a doctor whom he knew would be willing to prescribe lethally. That doctor referred her to a psychiatrist, who saw her once, and to a second doctor to confirm the terminal diagnosis. He also conducted a "three-sentence…cursory" discussion with the patient about alternatives to assisted suicide, such as hospice. When she voiced fears of being kept alive by artificial nutrition if she did not kill herself, the lethally prescribing doctor failed to assure her that she had the right to refuse such care—perhaps a crucial factor in her decision to swallow prescribed poison. The woman died a mere 2.5 weeks after her first meeting with the prescribing physician, during which time she was not in pain and she still looked after her house. That wasn't careful medical practice. It was pure Kevorkianism.

This first dismaying case was the start of a pattern. According to a study published in The New England Journal of Medicine of the first 15 legal assisted suicides, none of the other 14 cases involved people who were in unrelenting and irremediable pain and suffering. Rather, "the decision to request and use a prescription for lethal medication was associated with concern about loss of autonomy or control of bodily functions."[1] It also appears that, like the first case, many of the assisted suicides did not take place in the context of a meaningful relationship between patients and the doctors who wrote lethal prescriptions. Six of the 15 patients asked more than one doctor for the lethal prescription. At least one, perhaps more, had only a 15-day physician-patient relationship. As with the first case, it is highly likely that at least some of the doctors had close affiliations with assisted suicide advocacy groups, which raises a significant ethical issue. None of the assisted suicide cases seems to have involved the medical urgency of irremediable pain and suffering; thus the decision to prescribe lethal drugs appears, in at least some cases, to have been based on ideology.

Although two of the reported patients who committed assisted suicide were on Medicaid, which rations health care to the poor in Oregon, advocates touted the study's finding that money worries were not precipitators of the 15 deaths. It is hard to know if that was really true, since the best sources of information about the deceased patients—treating physicians who did not lethally prescribe and family members—were not interviewed. Besides, assisted suicide is still in its infancy, and these cases may not reflect an accurate prediction of how it would be practiced should it become routine.

Money may ultimately be the raison d'etre for legalized assisted suicide. With the advent of managed care, profits in health care increasingly come from cutting costs. What could be more cost-effective than assisted suicide? On the micro level, imagine the potential impact on families whipsawed between providing end-of-life care and sending children to college. Most families would do the right thing, but some would

undoubtedly look to "death with dignity" as the stone that kills two birds.

The public's support of assisted suicide is a vote of no confidence in the medical profession's ability to treat people in their dying days. But the "Oregon cure" is worse than the disease. It is now up to the medical profession to improve the quality of end-of-life care and prove that killing is not only wrong morally but medically unnecessary as well.

Wesley J. Smith is the author of Forced Exit: The Slippery Slope from Assisted Suicide to Legalized Murder (New York: Times Books/Random House; 1997). His next book will be Culture of Death: The Destruction of Medical Ethics in America.

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1 Quill TE. Death and dignity: making choices and taking charge. New York: WW Norton, 1994.

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Graduate medical education should not be overtaken by managed care

In the face of economic and political pressures, physicians must focus on healing the sick

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It is increasingly evident that the training of physicians in the 21st century will be influenced by pluralistic goals that may not be clinically oriented.[1] Among these influences is the aggressive intrusion of managed care on the lifelong professional commitment of physicians to their patients.[2] This circumstance threatens the essence of graduate medical education, which should be devoted to preparing competent physicians who can best treat their patients.

Traditionally, graduate medical education has been financially supported by two main sources: first, directly, by payments from Medicare, some Medicaid programs, and fees for hospital-based patient care services; and second, indirectly, by financial subsidies from grants, special patient care services (for example, head and spinal cord injuries and posttraumatic stress disorder), and the government's support for highly specialized technological medical care.

The first source of funding has been overtaken systemically by managed care companies or health maintenance organizations. Meanwhile the government's need to balance national budget policies is reducing the limited source of subsidized public funding. As a result, teaching hospitals and health sciences medical centers all across the country are struggling to maintain their residency training programs. Various mergers are anticipated between medical schools and privately owned corporations, the majority of them associated with health maintenance organizations.[3]

Although the health maintenance organization industry claims that it is striving to provide the most cost-effective and highest quality medical care, it is well known that most HMOs are run for profit. Likewise there are concerns that "managed care" may be a euphemism for "managed profit."[2-4]

If graduate medical education is to be affiliated with health maintenance organizations, then goals and long-term plans should be set up to ensure that its essential qualities are protected. The goals of graduate medical education are to train competent physicians who are able to diagnose, treat, cure, and prevent illness. This intensive task is "patient-centered" and follows the medical ethics of the Hippocratic tradition, founded on a trusting relationship between physicians and their patients.

The goals of health maintenance organizations are mainly managerial, based on cost containment through rigorous and impersonal preauthorization procedures. They are "product-oriented," and they minimize the importance of the patient-physician relationship. Under health maintenance organizations, physicians are labeled as providers or prescribers; patients are transformed into subscribers, customers, consumers, clients.[2,5]

Throughout the recorded history of the great civilizations of Egypt, Greece, and Rome, physicians were considered humanitarian professionals and were held in the very highest regard, equal to that of a priest, a minister, or a rabbi.[2,6] The history of health maintenance organizations shows businesses that strive to profit from health insurance premiums while denying medical care to the destitute and defranchised.[2,3] While physicians have always been paid fees for their services, they have historically provided the same quality care to wealthy and poor patients alike.[6]

To ensure that graduate medical education is not overtly influenced by health maintenance organizations, various goals should be set in place. The training of physicians must focus on providing the knowledge and the clinical expertise needed to diagnose, treat, cure, or prevent disease, regardless of the financial agenda of HMOs.

The physician-patient relationship must be preserved, not transformed into a negotiated financial contract between prescriber and purchaser.[1] Physicians need to be accountable only to their patients in regard to the quality and cost of their treatment, not pressured by third-party payers.[3,5]

The training of physicians should encompass social, psychological, and spiritual dimensions so as to treat each patient as a whole. Treatment should follow from physicians' clinical diagnoses, not mandated clinical guidelines that are based solely on cost savings.[1,5,6]

Physicians should be trained to practice evidence-based medicine, which is ultimately a cost-saving medicine.[7] Evidence-based medicine is the best argument against managed care's own brand of cost-effective medicine, which sometimes looks like "cutting-corners medicine."[7,8] Primary care physicians should be trained to provide primary care medicine and not gatekeeping medicine. The promotion of primary care specialties should not be achieved at the expense of reducing specialized medical training.[6,7]

Physicians should be trained to become their patients' most trustworthy and best devoted advocates while being involved in community medical care, which expands beyond the boundaries of their offices and hospital practices.[6] This tradition of care should not be delegated to allied healthcare providers.[9] Physicians should be trained to become leaders of multidisciplinary treatment teams. As leaders they are ultimately responsible for the total medical care of their patients; they are not just carriers of preauthorized prescription pads.[4,10,11]

If the healthcare financing administration, the Council of Graduate Medical Education, and the American Medical Association fail to resist the economic and political influences of HMOs and their intrusion on the shaping of the future of graduate medical education, then the practice of medicine as a trustworthy, competent profession may cease to exist.[10] If graduate medical education is taken over by HMOs, then medical schools and residency training programs may substitute the mission of mentors, professors, and academicians with that of other major players in the healthcare industry who are governed by insurers, providers, managers, and businessmen.[1,3,4,11]

For graduate medical education to survive the 21st century, it needs to cling to its intended mission of preparing physicians to heal the sick; it needs to resist being abducted by the political and economic powers of health maintenance organizations.

The author wishes to thank Ms. Tina Barry for her secretarial assistance.

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Terminal sedation for intractable distress

Not slow euthanasia but a prompt response to suffering

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Terminal sedation is the induction and maintenance of a sedated state with the intent of relieving otherwise intractable distress, both physical and mental, in a patient close to death. It is a way of providing relief to patients in the final phase of dying. In giving terminal sedation, the intent should focus on relieving distress, not deliberately hastening death.[1]

When other usual methods for relieving such suffering have failed, terminal sedation may be indicated for patients who suffer from either physical symptoms, such as pain or dyspnea, or mental distress. Often, during the final phase of dying, it is impossible to sort out physical from mental distress. Patients may be irreversibly delirious, a state that tends not to clear by withholding essential medications such as opioids for pain. While extreme distress and severe pain occur infrequently, lesser degrees of agitation and distress are more common. The frequency of symptoms at which sedation is appropriate is a topic open to debate.[2]

Informed consent should be obtained prior to initiating terminal sedation. The goals, benefits, and burdens of sedation should be discussed and documented. Most patients who could be appropriately considered for sedation will have already stopped eating and drinking, a nat-

ural occurrence in the final phase of dying. If sedation will interfere with eating or drinking, patients or their surrogates should be asked if they wish to decline artificial hydration while sedated. Most patients or surrogates will decline, as is their right to do so.

Only those medications that are absolutely necessary for the relief of symptoms should be continued. Opioids are commonly indicated for relief of pain and dyspnea and, if previously initiated, should be continued during sedation. Opioids should not, however, be used explicitly for sedation. They are poor sedatives, relying primarily on dose escalation for transient sedating effects.

A variety of agents can be used for sedation. Benzodiazepines are useful for mild agitation but may worsen delirium. Neuroleptics can be helpful, although care must be exercised in prescribing them for patients prone to seizures, as these drugs may lower the threshold for seizures. Chlorpromazine is particularly favored for terminal sedation as it is more sedating than other neuroleptics and has an anticholinergic effect that may help dry the respiratory secretions of terminal pneumonia, often present in the final stage of dying. Other sedating anticholinergic drugs, such as scopolamine, are commonly used in palliative care settings to dry secretions associated with terminal pneumonia. With these medications, sedation is often considered a welcome side effect.

It is not clear that terminal sedation, when used appropriately, significantly hastens death.

For most mildly distressed patients, the agents mentioned above will be adequate, but a small number of patients will need stronger medications. Barbiturates, midazolam, and anesthetics that are fast-acting, such as propofol and thiopental, have all been used for terminal sedation.[2] Palliative care specialists or, if they are unavailable, anesthesiologists can offer specialist advice.

When strong, short-acting agents are used, physicians should be present during the initial titration of the dose. In titrating the dose, the end point should be an observable effect: the elimination of audible signs of distress or movement such as grimacing or the appearance of sleep, for example. Once the dose necessary to induce an effect is determined, no further dose escalation should occur unless signs of distress reappear. Vague orders such as "Titrate drug X upward for comfort" are inappropriate. Without clear parameters and observable criteria for dose increases, dosing becomes subject to individual interpretation, resulting in confusion among staff as to what they are doing and why.

A distinction should be made between terminal and conscious sedation. Most hospitals have conscious sedation policies governing use of sedation during procedures, such as endoscopy. Such policies, usually requiring elaborate monitoring, should not apply to terminal sedation. Contrary to the expectation in conscious sedation, in terminal sedation it is expected (but not intended) that the patient will expire in the sedated state. Monitoring is intrusive and gives a conflicting message to staff and family as to the goals of care.

Terminal sedation is a relatively new approach to treating terminal distress. Not all members of the care team or family may understand or agree with the rationale or the methods used. Great care should be taken to involve all parties working with the patient, as discord among team members can be sensed by the family and even by the patients themselves, which creates additional distress and may hinder the effects of sedation. A peaceful environment is critical to the success of terminal sedation.

Concern has been expressed that without guidelines for the use of terminal sedation, the procedure might be subject to abuse.[3] Indeed, clearer guidelines do need to be developed. Some believe terminal sedation is really a form of slow euthanasia, arguing that death is hastened by inducing dehydration.[3,4] Most patients appropriate for terminal sedation, however, will have already stopped eating and drinking.[5] The rare patient who meets the suggested criteria for terminal sedation and is still eating and drinking may well decline artificial hydration, and the physician has no right to override this decision. If dehydration were to hasten death in such a case, it would result from the patient's and not the physician's actions and thus not qualify as euthanasia.[6] Aside from this potential scenario, it is not clear that terminal sedation, when used appropriately, significantly hastens death. To the extent that death might be hastened, this consequence should not be considered the intent but rather a side effect of sedation, accepted after carefully weighing benefits and burdens of sedation.

If we are to be sincere in our pledge to keep patients comfortable at the end of life, as patients and families frequently ask us to do, we must become proficient in methods such as terminal sedation that ensure our ability to provide such comfort when other approaches fail.

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The future of hospice

Unshackle from per diem reimbursement and the six-month limit on prognosis

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A 47-year-old man is referred for hospice services with advanced amyotrophic lateral sclerosis. He has two teenaged children; his wife works part time. His physical deterioration over the past three years is well documented. Once lifted into his motorized wheelchair, he has some mobility around the house. His respiratory mechanics fall within the "guidelines for referral." His secretions are managed by suctioning, and his periodic/nocturnal dyspnea responds well to noninvasive continuous positive airway pressure. The cost of this last therapy alone is $1,120 per month.

Providing care for such a patient is one tiny fraction of the challenge faced by hospice programs today as they seek to redefine their place in America's healthcare systems. Many of these dilemmas are generic and can be counted off like rosary beads. They include inadequate or constrained access to health care in general, deficiencies in healthcare professionals' training and commitment to end-of-life issues, and long-standing, ingrained barriers to pain management and symptom management. All these dilemmas stand forth against a background of reimbursement streams and incentives that often conflict both pragmatically and philosophically with hospice efforts.

But some predicaments specific to hospices are of their own creation. In 1982, hospices made a devil's bargain with the federal government. In exchange for what was then a life-saving stream of revenue, they accepted two conditions of participation: they would only accept patients with a prognosis of 6 months or less and they would operate on a per diem payment schedule. The net effect has been to define hospice care in the public and professional mind as being more for the brink of death than for the end of life, with average lengths of stay around 36 days and median lengths of stay about 15 days. Within the rigid construct of this regulatory box, most hospices have found the fiscal constraints of reimbursement so confining that they are reluctant to admit patients whose conditions might not follow the predictable trajectories of malignant disease, or to support expensive and labor-intensive therapies such as continuous positive airway pressure. Reluctance arises especially when the hospice is treating patient populations with special needs, such as children, people with AIDS, the poor, and those who live alone.

Hospice is generally acknowledged to be the exemplary model of palliative care. It follows, then, that it is in the best long-term interest of hospice to unshackle itself from the default position of having to make the terrible choice between curative and palliative care. Studies should provide evidence that efficacy and efficiency in care can be gained by dissembling or waiving the requirement that every hospice patient must have a 6-month prognosis. In addition, studies should consider the effects of eliminating fixed per diem reimbursements and evaluate alternatives, such as variable payment based on acuity and length of stay or provision of services under the cap regulations that already exist. Such models are intuitively appealing, as they adjust for the exponential increases in drug and other fixed costs to hospices far more coherently than the surreal "cost-of-living" methodologies presently used.

These studies will need to be funded by the usual sources—government, educational institutions, and foundations—but they will also need to be championed by the leadership of all hospice constituencies. If studies demonstrate the benefits of new approaches to hospice care, their results will broaden the reach of hospice services to the greatest number of patients, families, and populations, yet hospice organizations will still fulfill their fiscal responsibilities. Such studies will encourage hospice to continue innovative care delivery, which has been the root of its success, and to integrate the precepts of palliative care further upstream in the healthcare system.

They will, in short, allow hospice to unhoist itself from its own petard.

Netphiles

Readers are referred to a website from the state of Oregon that makes available information and statistics concerning participation in legal physician-assisted suicide. The address is: http://www.ohd.hr.state.or.us/cdpe/chs/pas/pas.htm.

Mail

Hospital staff do not know how much drugs cost

To the Editors,

The major portion of a hospital budget is spent on medicines. With drugs becoming increasingly expensive, it is important to have a rational policy for using essential drugs.[1,2] The goal of cost containment cannot be achieved if it is not supported by staff awareness. Recent articles have highlighted the poor awareness of hospital staff about the cost of drugs.[3]

A survey was conducted at Ispat General Hospital, Rourkela, in Central India, a referral hospital attached to the steel industry. The hospital has 101 doctors and 224 nurses. We asked 29 nurses and 42 doctors who were attending a departmental meeting to participate in our survey on cost awareness.[4] Staff associated with stores or the purchasing committee were excluded. Staff were provided with a questionnaire that asked the cost of 15 common hospital items, such as ranitidine, diclofenac, intravenous infusions, disposable items such as urinary catheters, and tests such as an ultrasound examination of the abdomen.

Cost predictions within 20% of the correct price were considered acceptable. Predictions beyond that were considered incorrect and classified as either an overestimate or an underestimate. In this survey, 41% of the responses were incorrect—24.3% were overestimates and 16.7% were underestimates. Of the physicians' responses, 25.1% were overestimates and 20% were overestimates. Of the nurses' responses, 23.2% were overestimates and 11.9% were underestimates.

The doctors had a greater awareness of the price of common medicines, such as antihypertensive drugs, antacids, antibiotics, and analgesics. But their perception of the costs of investigations, bed charges, or disposable items was poor. The nurses had a clear idea about the charges related to different investigations and procedures such as radiographs, biopsy tests, and intravenous fluids.

The doctors could predict better than the nurses the prices of antacids (50% vs 24.2%) and antihypertensive drugs (45.5% vs 17.3%). The nurses had a better awareness of the cost of dextrose infusions (75.9% vs 40.5%), plasma expanders (58% vs 21%), and urinary catheters (62.1% vs 31%).

Both underestimates and overestimates affect healthcare services. If the price is underestimated, then the chance of waste will be more. When the charges are overestimated, use may be compromised at times. Both miscalculations are detrimental to good clinical practice and health budgeting.

In a recent study from Sierra Leone,[5] it was observed that doctors tended to prescribe more proprietary brand names than the generic names. Doctors are well informed about the proprietary brand names through distribution of free samples and brochures and through the organization of seminars by the manufacturers. Thus doctors tend to prescribe brand name medications rather than generic drugs.

Doctors need more accurate information than that given to them by medical representatives. Without education, cost containment cannot hope to be successful.

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Traditional case reports still have a role

To the Editors,

In his effort to promote the journal's evidence-based case reviews, Dr. Hoffman underplays the importance of traditional case reports.[1] In addition to the three types of case reports discussed by him, there are others that have merits. There are numerous examples of severe side effects of drugs that were detected only after the drugs were licensed. Recognition of these side effects was often triggered by a single case report, followed by several others. The public health importance of such case reports is unquestionable. Some case reports, in which patients are taken off drugs and then rechallenged by being put back on them, can establish a causal relationship between the exposure to the drug and the outcome. This is something that more sophisticated study designs can sometimes fail to achieve.

Side effects due to the interaction between drugs, or due to the use of drugs in patients with renal failure, have also been recognized through case reports. Case reports have been responsible for the recognition of false reports of laboratory test abnormalities when these tests were performed in patients taking certain drugs.[2] A supposedly rare clinical manifestation not cited in modern textbooks was observed in a patient, and a review of the literature showed that this had been noted previously in a case report.[3]

Dr. Hoffman argues that case reports that describe a rare condition are of no use to most clinicians, and that those who need such information could get it from textbooks. In the modern world, with large data sets of medical articles available—sometimes free of charge—from the internet (such as MEDLINE), an increasing number of physicians can easily access papers, including case reports, published in many peer-reviewed journals. Thus information can be obtained perhaps more easily from published reports than from textbooks. And one should not forget that authors of textbooks use case reports as sources of information.

I consider the evidence-based case review by Wilkes and colleagues[4] as a step forward. I do believe, however, that traditional case reports still have a role in medical literature, perhaps even as a source of evidence for evidence-based case reviews.

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Author's response

Dr. Nishioka points out that a case report can be the first place in which an important adverse effect of some new drug is identified. Although the wrinkle is a bit different, the substance of this "adverse effect" type of report is basically similar to the "new treatment" type of report I described, and which I acknowledged is occasionally valuable. As in this latter case, the case report that considers an "adverse effect" deals with a previously unobserved phenomenon and can stir further inquiry or observation and lead to a beneficial change in practice if subsequently confirmed.

As with the "new treatment" case report, however, it too can do more harm than good, as an observed "relationship" in a single case may very well prove to be inaccurate and/or misleading. Case reports of major depression due to reserpine, for example, led to the general abandonment of an effective, inexpensive, and safe drug, because the problems seen with using excessive doses were inappropriately extrapolated to the standard doses in general use.

With chloramphenicol, descriptions of (extraordinarily rare) cases of irreversible aplastic anemia were accurate, but they too surely caused harm, by virtually eliminating the use of a drug for various life-threatening infections for which there were (at that time) no equally effective alternatives.

Dr. Nishioka also notes that the textbooks and experts to whom I suggest we look for advice regarding rare diseases may also make use of case reports. Clinicians should certainly retain a healthy skepticism when being preached to by experts. But when information on a topic is scanty, and limited to isolated observations, those who deal most often with rare diseases should have the best chance to put such observations into context and evaluate their clinical significance.

We are frequently told that information is power and that any information is always better than no information at all. But information is not useful if it is distorted, or misleading, or easily misinterpreted, or unrepresentative—as case reports by their nature often are. Perhaps abandoning case reports altogether would not be a good idea, but I doubt that this will happen soon in medical publishing, my editorial notwithstanding! In the meanwhile, readers should at least consider their substantial limitations.

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capsule

Why slimmers can't stay slim There is still fierce debate on why slimmers often fail to stay slim. A meta-analysis that tries to make sense of a quagmire of fairly poor research concludes that people who have been obese have a lower resting metabolic rate than controls (American Journal of Clinical Nutrition 1999:69:1117-1122). An accompanying commentary, however, concludes the opposite from the data, that an obesogenic environment is responsible for making slimmers fat again. Part of the problem is that only 124 formerly obese people have ever been studied, which is too few to conclude anything.

Original Research

The effectiveness of glucocorticoids in treating croup: meta-analysis

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ABSTRACT **Objective** To determine the effectiveness of glucocorticoid treatment in children with croup. **Design** Meta-analysis of randomized controlled trials that examine the effectiveness of glucocorticoid treatment in children with croup. **Main outcome measures** Score on scale measuring severity of croup, use of co-interventions (epinephrine, antibiotics, or supplemental glucocorticoids), length of stay in the emergency department or the hospital, and rate of hospitalization. **Results** Twenty-four studies met the inclusion criteria. Glucocorticoid treatment was associated with an improvement in the croup severity score at 6 hours with an effect size of –1.0 (95% confidence interval [CI] –1.5 to –0.6) and at 12 hours –1.0 (–1.6 to –0.4); at 24 hours, this improvement was no longer significant (–1.0, –2.0 to –0.1). There was a decrease in the number of epinephrine treatments needed in children treated with glucocorticoids: a decrease of 9% (95% CI 2% to 16%) among those treated with budesonide and of 12% (4% to 20%) among those treated with dexamethasone. There was also a decrease in the length of time spent in the emergency department (–11 hours, 95% CI –18 to 4 hours) and, for inpatients, hospital stay was reduced by 16 hours (–31 to 1 hour). Publication bias seems to play a part in these results. **Conclusions** Dexamethasone and budesonide are effective in relieving the symptoms of croup as early as 6 hours after treatment. Fewer co-interventions are used, and the length of time spent in the hospital is decreased in patients treated with glucocorticoids.

Croup (laryngotracheobronchitis) is a common cause of upper airway obstruction in children and is characterized by hoarseness, a barking cough, and inspiratory stridor. These symptoms are thought to occur as a result of edema of the larynx and trachea triggered by a recent viral infection. Parainfluenza virus type 1 is the agent most commonly identified in cases of croup.[1]

Although croup is a self-limiting illness, it places a large burden on healthcare systems because of the frequent visits made to doctors and emergency departments and, when necessary, the hospitalizations. The annual incidence of croup in children younger than 6 years ranges from 1.5% to 6%.[2] Admission rates for croup in children seen in outpatient settings range from 1.5% to 31% of cases seen; these figures vary widely, depending on hospital admission practices and the severity of the disease in the population being assessed.[3,4]

The standard management of croup includes mist treatment (that is, treatment with humidified air), although there is little evidence that it is effective.[5] Racemic epinephrine, or L-epinephrine, has been shown to provide temporary relief to patients with croup but is not thought to have longer-term benefits.[6] Since the late 1980s, it has been recognized that glucocorticoids provide some clinical benefit in children with croup. In 1989, Kairys et al. published a meta-analysis of clinical trials examining the benefit of glucocorticoids.[7] Since then, however, a number of randomized trials have been published, and there has been increasing interest in the use of glucocorticoids to treat outpatients with croup. The objective of our meta-analysis was to provide evidence to guide clinicians in their treatment of patients with croup, to examine the effectiveness of glucocorticoids in these patients, and to identify areas of uncertainty for future research.

Summary points

- Most trials evaluating the treatment of croup are of high methodological quality and hence have a low risk of bias.
- Publication bias seems to be a problem, however, making the results of this meta-analysis somewhat less certain.
- Glucocorticoids seem to bring about clinical improvement within 6 hours in children with croup.
- Nebulized budesonide or dexamethasone, given either orally or intramuscularly, is effective in treating croup.
- The use of glucocorticoids is associated with a lower rate of use of co-interventions and shortens the time spent in the hospital.

METHODS

Study protocol

A protocol was developed and approved by the Acute Respiratory Infection Control of the Cochrane Collabora-

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Competing interests: D.W.J. received research funding from Astra Pharmaceuticals, the manufacturer of budesonide, to complete a trial comparing treatment with budesonide, dexamethasone, and placebo.[w12]

This paper was originally published in the BMJ 1999;319 (7210):595-600. Those references for the trials included in this study that are prefixed with the letter "w" can be found on the BMJ's website at: www.bmj.com.

tion and is published in the Cochrane Database of Systematic Reviews (CDSR). The full review will be published in the next issue of CDSR.

Study identification

We searched MEDLINE from January 1966 to August 1997, exploring glucocorticoid treatment (and each of the terms for corticosteroids) and croup; we restricted the search to randomized controlled trials using a previously validated strategy (see Appendix 1 on the BMJ's website, www.bmj.com). We searched Excerpta Medica and Embase from January 1974 to August 1997 (Appendix 1). The Controlled Trials Register of the Cochrane Library was also searched; it includes studies identified by the Acute Respiratory Infection Review Group through the hand-searching of key journals. We also sent letters to the authors of trials published in the past 5 years to inquire whether they knew of any other published or unpublished trials. Two researchers (T.P.K., M.A.) then selected the studies that were potentially relevant, based on a review of the titles and abstracts, if available. The complete text of these studies was then retrieved.

All studies that had been retrieved were reviewed independently by two reviewers (A.S., T.P.K.). To be eligible for inclusion in this review, a study had to meet all of the following criteria: it had to have studied patients with croup; an intervention with glucocorticoid had to have been compared with either placebo or any other active treatment; clinically relevant outcome measures had to have been used, such as the clinical score, hospitalization rate (in outpatient studies only), length of time in hospital, or additional interventions used; and patients had to have been randomly assigned to treatment groups. Studies written in any language were eligible for inclusion. The weighted κ score was used to measure interrater agreement. Differences over which studies should be included were resolved by consensus reached after discussion.

Data extraction

Once we identified studies as being relevant for review, they were masked by obscuring the authors' names and institutions, the locations of the studies, reference lists, and any other potential identifiers. The masking was done by an independent research assistant who was not involved in the abstraction of data. Data were extracted using a structured form that captured patient status (inpatient or outpatient), the intervention and its control, the name of the drug, the route of administration, and the dose. Additionally, data were collected on the primary outcome measure; clinical croup score at baseline and at any subsequent assessment times; length of stay in the hospital or the emergency department, expressed in hours; whether the patient had improved (coded yes or no); and the use of additional interventions such as epinephrine, supplemental glucocorticoids, mist treatment, intubation, or antibiotic treatment. Data were extracted by one reviewer (M.A.) and checked for accuracy by a second reviewer (T.P.K.).

Quality assessment of trials

We assessed quality using empirically derived items. We used the previously validated Jadad five-point scale to assess randomization (0-2 points), double blinding (0-2 points), and withdrawals and dropouts (0-1 point).[8] For component assessment, concealment of allocation was described either as adequate, inadequate, or unclear.[9] Sponsorship of studies was coded as either pharmaceutical company, other sources, or not mentioned.[10] Two observers independently assessed quality (M.A., J.D.K.), and inter-rater agreement was measured by the intraclass correlation.[11] Differences were resolved by consensus.

Data analysis

All comparisons were performed between treatment and control groups, thus preserving randomization. The main outcome measure was the difference between treatment groups in the mean change from croup score at baseline. We derived the outcome measures from cross-sectional summaries (for example, at baseline, 6 hours, and 12 hours) in cases in which outcome measures were not reported directly. The variance of an effect size was derived from the common variance of a single croup score, assuming a correlation of 0.5 between pretreatment and posttreatment scores. Other variance imputations were performed according to the work of Follman et al.[12] Variances of a single score were derived from the P values of the Mann-Whitney test[w8,w9,w23] and from the measurement of confidence intervals.[w4] (References starting with "w" will be found on the BMJ website.)

The croup score was reported inconsistently because of the different scales used in each study, hence trial effect sizes were used in the pooled estimates.[13] A treatment effect divided by its measurement variation (for example, a pooled standard deviation) gives an effect size. To aid in the interpretation of pooled results reported by standardized effect size, we converted the effect size scale back to the croup score, using a subset of trials in which such scores were available. Another way to express the croup score is by determining a clinically important change in the score in the individual patient and then calculating the proportion of patients who had significant improvement among the patients treated with glucocorticoids or placebo.

In addition to funnel plots, we used the rank correlation test[14] and a graphical method[15] for the detection

of publication bias.[16] Adjustment for publication bias in the pooled estimates was performed using the graphical method,[15] a selection model approach,[17] and the trim and fill method.[18] We used more than one method, because the relative merits of the various methods are not well established. Tests of homogeneity were performed with the χ^2 statistic for between-study variation.[13] For the analyses of croup scores and secondary outcomes, fixed effect models were used to combine treatment effects if there was no evidence of heterogeneity across studies; otherwise, the more conservative estimates from random effect models were reported. For binary data (such as improvement in signs and symptoms and the presence of various additional interventions), rate differences and the number needed to treat were derived. For the number needed to treat, we inverted the differences in the proportions improved and their 95% confidence intervals.

Heterogeneity between studies was explored using sensitivity and subgroup analyses performed on the primary outcome of the change in croup scores from baseline at 6 hours. Westley scores were the scores most commonly used in the trials.[19] Westley scores use a 17-point scale to assess air entry (2 points), stridor (2 points), intercostal retractions (drawing in of the chest wall between the ribs on inspiration) (3 points), cyanosis (5 points), and level of consciousness (5 points). Treatment differences in Westley scores were calculated in place of effect sizes to provide an approximate conversion between the two scales. Differences between estimates derived from Westley and other scores were assessed.

A trial effect size was defined as the difference between the two treatments in the mean change from croup score at baseline. We derived effect sizes from cross-sectional summaries (for example, at baseline, 6 hours, and 12 hours) for trials not reporting effect sizes directly. The standardized effect size (that is, an effect size divided by the common standard deviation of the change from baseline) was used to combine trials reporting different versions of the croup score. Sensitivity analyses were based on the type and dose of glucocorticoid administered. The quality score of the included trials was incorporated into the pooled estimates, using the method proposed by Moher et al.[20] In addition, the impact of the concealment of treatment allocation on the pooled estimates was assessed.[9]

RESULTS

Study identification and characteristics

Ninety-seven studies were identified as potentially relevant and thus retrieved. Two of these studies were in press at the time of data extraction and have since been published.[W11,W13] Forty-four studies were excluded because they were reviews or commentaries. Twelve did not study croup. Nine had inadequate randomization strategies. Four were retrospective studies, two had no control group, one had no outcome of interest, and one was a duplication. Therefore, 24 studies were included (references and full details of these studies can be found in Table A on the BMJ website). The weighted κ score between two reviewers was 0.89, indicating substantial agreement.

Twenty-two of the included studies had been published in English, one in French, and one in Spanish. Dexamethasone was evaluated in 17 trials, budesonide in 9, and methylprednisolone in 3. Some studies examined more than one drug. Five of the trials compared active treatments; 19 were placebo-controlled. The mean age of the children in the different studies ranged from 13 months to 45 months; the minimum age was 4 months and the maximum age was 12 years. Fourteen trials were conducted on inpatients; 10 were conducted on outpatients. Studies tended to be small, however, with a median of 40 participants (interquartile range 36 to 60). The pooled baseline rates using fixed effect models were reported.

Quality assessment of trials

The intraclass correlation between two reviewers was 0.63 for the Jadad scale, 0.98 for allocation concealment, and 1.0 for sponsorship, indicating at least substantial agreement in all cases. The median Jadad score was 3 (interquartile range 2.75 to 4) or 60% (55% to 80%) for the best quality of reporting. Allocation concealment was adequate in 11 (46%) of the studies, inadequate in 1 (4%), and unclear in 12 (50%). Pharmaceutical sponsorship was identified in 3 (13%) studies, support came from other sources in 3 (13%), and support sources were not mentioned in 18 (75%). Overall, the quality of studies was better than has been observed for other diseases.[9,20,21]

Croup score

The most frequent outcome utilized in 13 studies was the clinical croup score, based on a 17-point ordinal scale developed by Westley.[19] Other scoring systems, none of which have been validated, were utilized in five studies; in six studies, no clinical score was reported.

The improvement in the Westley croup score at 6 hours was 2.8 (95% confidence interval [CI] 2.2 to 3.5) for dexamethasone or budesonide versus 1.0 (0.3 to 1.7) for placebo. The difference in improvement in the Westley score between treatment arms at 6 hours was 1.6 (1.1 to 2.2). The pooled standardized effect size was 1 (0.6 to 1.5) at 6 hours and 1 (0.4 to 1.6) at 12 hours. From our data, a standard effect size of 1.2 (0.7 to 1.7) corresponded with an improvement of 1.6

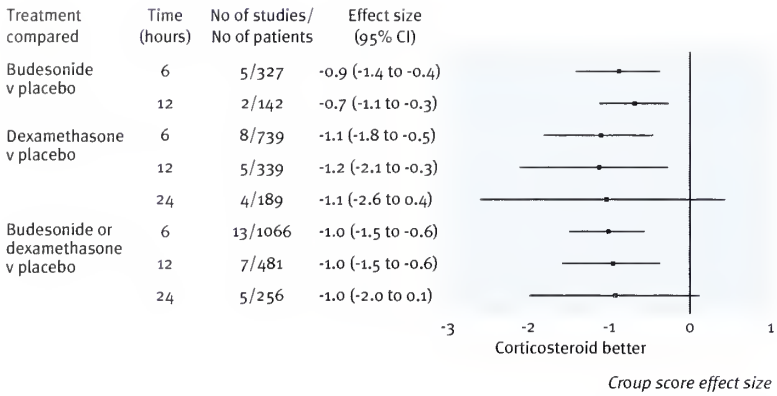

Figure 1 *Pooled effect sizes (95% confidence intervals) of glucocorticoid treatment for croup versus placebo. All estimates had significant heterogeneity among trials.*

(1.1 to 2.2) in a Westley score (see Figure 1; also see Appendix 2 on the BMJ website for a list of included trials). This change was not significant at 24 hours; fewer patients were evaluated at 24 hours, however, and hence the lack of significance may be a reflection of a lack of statistical power. The magnitude of change of –1 is similar to that seen at earlier evaluation points, but the 95% confidence interval crosses zero. A decrease in effect size of one from baseline is thought to be a clinically important change.

At 6 hours, the difference in risk was 15% (95% CI 2% to 28%) with a number needed to treat of 7 (4 to 50). The baseline rate of clinical improvement was 41% (32% to 50%). At 12 hours, the risk difference was 21% (9% to 33%) with a number needed to treat of 5 (1 to 11). The baseline rate of clinical improvement was 68% (58% to 77%). At 24 hours, the risk difference was 12% (3% to 22%) with a number needed to treat of 8 (5 to 33). The baseline rate of clinical improvement was 83% (75% to 91%). Although not all studies contributing to the effect size expressed their results as improved versus not improved, the degree of benefit of a number needed to treat of 5 to 7 patients (at different assessment times) would be sufficient to support the use of glucocorticoids over placebo.

Additional interventions

There was no significant increase in the use of antibiotics among those treated with glucocorticoids as compared with those treated with placebo when expressed as the difference in risk. This result was consistent for the dexamethasone group (4%, –20% to 27%) and the budesonide group (–2%, –17% to 13%). There was a significant decrease noted in the use of epinephrine in the glucocorticoid groups, with a difference in risk of –9% (–16% to –2%) in the budesonide group (number needed to treat 10; baseline rate 16%) and –12% (–20% to –4%) in the dexamethasone group (number needed to treat 8; baseline rate 23%). There was no significant impact on the use of supplemental glucocorticoids among either those treated with dexamethasone (4%, –4% to 13%) or those treated with budesonide (–15%, –32% to 2%).

When any glucocorticoid was compared with placebo (11 studies, 1150 patients), there was no significant change in the rate of difference of intubation or tracheotomy –2% (–14% to 10%; baseline rate 3.2%, 2.9% to 3.5%).

Hospitalization

Overall, a significantly shorter time was spent in the emergency department when children were treated with a glucocorticoid as compared with placebo (5 studies, 596 patients); the weighted mean difference was –11 (–18 to 4) hours. For inpatients, the difference was –16 (–31 to 1) hours.

There was a nonsignificant decrease of –16% (–39% to 6%) in the rate of hospitalization for patients treated with budesonide versus patients treated with placebo (baseline rate 32%, 24% to 39%). This was also true for patients treated with dexamethasone as compared with patients treated with placebo (–2%, –31% to 5%) or if any glucocorticoid was compared with placebo (–14%, –12% to 5%). The more conservative random effects model was used to derive the overall estimate of the difference in hospitalization rates, because there was significant heterogeneity between studies. If the fixed effects model estimate was used, there was a significant decrease in hospital admissions between patients treated with budesonide and those treated with placebo (–15%, –20% to –10%).

Sensitivity and subgroup analyses

The sensitivity analysis showed that the method of scoring the severity of croup was important (see Figure 2). An effect size of –1.2 (–1.7 to –0.7) was identified when the Westley croup score was used (9 studies, 569 patients), as compared with an effect size that was 50% smaller (a size that was no longer significant) when other croup scores were used (4 studies, 497 patients; –0.6, –1.5 to 0.3). The Westley score is the only method that has undergone validation and reliability testing and been shown to be sensitive to important changes in a patient's clinical status. The smaller treatment effect noted with non-Westley scores could reflect either sensitivity to change or a greater degree of variability caused by low reliability.

We were unable to compare the route of administration of glucocorticoids in a meaningful way because of the lack of standardization of scores between studies. The quality weighting of the effect size did not change the estimate or the width of the 95% confidence interval; this result is in part explained by the high methodological quality of the studies. The estimate derived from studies in which allocation was adequately concealed was –1.2

(–1.9 to –0.5), and for the studies in which it was inadequately concealed or in which it was unclear, it was –0.9 (–1.4 to –0.3). These differences are probably not clinically or statistically significant.

Publication bias

We identified a marked publication bias. There is also the possibility that small studies showing that glucocorticoids had no effect were suppressed from publication. There was a significant correlation between treatment effect and sample size (for example, rank correlation test P=0.013; graphical method P=0.004). The Dear-Begg estimate of this correlation was 0.29. Pooled effect size at 6 hours, calculated using the simple graphical method, was –1.1 (–1.5 to –0.8); with the selection model, it was –1.2 (–2.4 to –0.01); and with the trim and fill method, it was –0.2 (–0.8 to 0.4). The trim and fill method suggested that seven small trials were suppressed because their results were not significant.

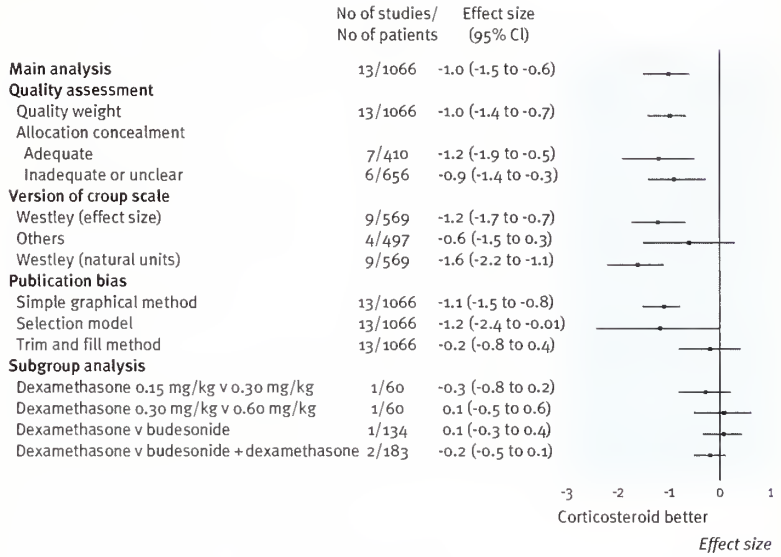

Figure 2 *Sensitivity and subgroup analyses of change in croup score from baseline at 6 hours. Negative effect sizes indicate relative improvement with glucocorticoid treatment.*

DISCUSSION

Efficacy of steroids

This meta-analysis has shown that treatment with glucocorticoids is effective in improving symptoms of croup in children by as early as 6 hours, and for up to at least 12 hours, after treatment. This is shown by the significant improvement in scores of croup severity, by shorter hospital stays, and by the fact that epinephrine was used less often as an additional intervention. Although the decrease in the rate of hospitalization was not significant, this outcome criterion varies from hospital to hospital, and the direction of the change was toward effectiveness. The degree of benefit identified would merit the use of glucocorticoids, since from five to seven patients would need to be treated with glucocorticoids for one patient to experience a significant improvement in symptoms.

This finding did not change when the quality of the studies included was incorporated into our pooled estimate. We found a significant improvement, even though almost half of the patients included were assessed using scoring tools that have not been validated and may be less sensitive to important changes in the patient's clinical status.

Publication bias

Of more importance is the fact that publication bias seems to be a modifier of this result, and it is likely that our analysis did not include smaller studies that had statistically negative results. Publication bias is an important threat to the validity of systematic reviews and is difficult to combat except through the registration of all randomized controlled trials on human participants. The existence of this bias suggests that this meta-analysis may overestimate the effectiveness of treatment with glucocorticoids. The results indicate that, to experience improvement, the number needed to treat at 12 hours is five patients for one patient. If publication bias exists and has exaggerated the benefit of treatment, then the number needed to treat would be greater. Thus clinicians will have to decide whether it is still worth treating patients for croup. Considering the comparative safety and low cost of dexamethasone, it probably makes sense to continue using glucocorticoids. In cases in which the effect of adopting treatment with glucocorticoids has been examined, there has been evidence for a decline in hospital admission rates, fewer admissions to the intensive care unit, and shorter lengths of stay.[22,23]

The small numbers of patients in each study and confounding variables make it difficult to express definitive recommendations regarding the superiority of any glucocorticoid, dose, or route of administration. In the absence of further evidence, an oral dose of dexamethasone, probably 0.6 mg/kg, should be preferred because of its safety and efficacy. In a child who is vomiting, nebulized budesonide or intramuscular dexamethasone might be preferable.

Our results are mostly consistent with those of the meta-analysis by Kairys et al., which found that glucocorticoids are beneficial in patients with croup,[7] but there are some important differences. Because of the lower probability of bias in such studies, we included only randomized controlled trials; hence some studies that were included by Kairys et al. were not included in our meta-analysis. These excluded studies tended to be older and used techniques of quasi-randomization, such as alternate allocation.[24-26] Additionally, 15 randomized controlled trials on this topic have been published since 1989,

many of them outpatient trials examining the effectiveness of budesonide or dexamethasone. The differences between inclusion criteria in our meta-analysis and that by Kairys et al. may account for Kairys's finding that glucocorticoids significantly decrease the risk of intubation, which we did not observe.

Study quality

The quality of the studies included was good. The median Jadad score in our study was three; in other studies, the median is often two or less.[20,21] In 46% of the trials, allocation was adequately concealed; in most other studies, about 10% to 15% of the trials being assessed have adequate concealment.[9,20] Although quality assessment and methods of its incorporation into systematic reviews are controversial, we have recently shown the importance of such assessments in detecting bias and have proposed a method of quality weighting.[20]

Outcome measures

Outcome measures are important in detecting significant change in a patient's clinical status. It is important that this measure is valid (that it measures what it ought to) and responsive (that it is sensitive to change).[27] This meta-analysis supports the importance of using valid and responsive outcome measures, since the magnitude of the effectiveness of the treatment in this study was dependent on which scoring method was used. We have shown that the Westley score is valid, responsive, and a reliable measure.[28] Although further validation and modification could be made to the Westley score, it should remain the primary outcome measure in trials currently being conducted.

Future trials may want to explore which dose of dexamethasone is most effective: is 0.15 mg/kg really as effective as 0.6 mg/kg? This meta-analysis supports the use of glucocorticoids to treat any patient with croup who has any signs of respiratory distress.

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Contributors: M.A. and A.S. were responsible for most of the project management and for retrieving articles, assessing their relevance and quality, and extracting data. They also helped with writing the paper. B.P. helped with data management and statistical analysis. D.M. helped in reaching the consensus decisions on relevance and quality assessment and provided methodological support and editorial comments. J.D.K. assessed the quality of trials included and provided methodological support and editorial comments on the paper. T.P.K. helped assess studies for their relevance for inclusion, checked the data for accuracy, and helped write the paper. Annie Walker, of the Child and Youth Clinical Trials Network, assisted in the preparation of this article. T.P.K. is the guarantor for the study.

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COMMENTARY

Demonstrated benefit of glucocorticoids does not mean prednisone is beneficial in the routine office setting

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In a recent meta-analysis, Klassen et al. attempted to determine the effectiveness of glucocorticoid treatment in children with croup by combining the results of 24 randomized trials. The major outcome measures were croup severity score, use of cointerventions, length of stay in the emergency room setting, and rate of hospitalization. The study showed that use of oral or intramuscular dexamethasone or nebulized budesonide resulted in a 1-point decrease in the Westley severity score, a 10% absolute decrease in use of adrenaline, and nonsignificant decreases in emergency room stays (by 11 hours) and inpatient stays (by 16 hours).

In children with croup who are admitted as inpatients, steroid use has become the standard of care. The major question for pediatricians and emergency room physicians is, to which patients in the outpatient setting should they administer steroids? Should they be giving steroids to all children who present with croup? This study suggests that steroids can have a beneficial effect in many patients.

The main finding of this meta-analysis of glucocorticoid use was an improvement in the croup score, a composite rating of level of consciousness, color, stridor, air entry, and retractions at both 6 and 12 hours (see box).[1] A drop of 1 point on the Westley 17-point scale would be clinically significant in a child with mild to moderate symptoms but unlikely to affect the rate of intubation or tracheostomy in severely ill patients, as this study also showed. For the practicing physician, glucocorticoids represent an additional helpful mode of therapy but not a panacea. Furthermore, it is not clear from the meta-analysis at what initial croup score patients were eligible for the randomized trials included in the analysis. The answer could help determine exactly which children with croup should be considered for this treatment.

The use of adrenaline was significantly decreased in the groups that received glucocorticoids. In emergency room settings, this decrease has special significance. Children who receive racemic epinephrine in the emergency room must be observed for 4 hours before discharge to ensure that they will not experience a "rebound" effect; this requirement results in longer patient stays. If the use of adrenaline is decreased, patient time in the emergency outpatient setting may be significantly reduced.

Westley Clinical Scoring System

Level of consciousness	
Normal (including sleep)	0
Disoriented	5
Cyanosis	
None	0
Cyanosis with agitation	4
Cyanosis at rest	5
Stridor	
None	0
When agitated	1
At rest	2
Air entry	
Normal	0
Decreased	1
Markedly decreased	2
Retractions	
None	0
Mild	1
Moderate	2
Severe	3

Extrapolating from the available data, many physicians are now treating croup in their offices with oral courses of prednisone. It is important to recognize that in the randomized trials included in this meta-analysis, only dexamethasone or nebulized budesonide were used as treatments. It cannot be assumed that because these results show glucocorticoids to have a beneficial effect, prednisone treatment is indicated or beneficial in the routine office setting. And because nebulized budesonide is not approved for treatment of croup in the United States, oral or intramuscular dexamethasone would be the preferred mode of steroid administration in these patients.

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capsule

Acne hurts Acne may be common, but it is not trivial. A team of British epidemiologists and dermatologists compared the health and well being of 111 patients with moderately severe acne with a random sample of over 9000 people (British Journal of Dermatology 1999;140:672-676). The patients with acne reported worse mental health and social problems than controls with asthma, epilepsy, diabetes, back pain, or arthritis. Acne is an unfashionable disease that deserves more attention and, of course, more money, they conclude.

Pharmaceutical advertising revenue and physician organizations: how much is too much?

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ABSTRACT **Objective** To determine if revenue generated from pharmaceutical advertisements in medical journals creates potential financial conflicts of interest for nonprofit physician organizations that own those journals. **Design** Convenience sample of six professional medical societies and their respective journals. Calculation of pharmaceutical advertising revenue generated by these journals for their respective professional medical societies. **Methods** Random selection of each journal for one month per quarter in calendar year 1996 and tabulation per edition of the average number of pharmaceutical advertising pages for each journal. **Outcome measures** Published advertising rates were used to estimate pharmaceutical advertising revenue for calendar year 1996 and compared with each organization's gross revenue and membership dues and assessments, based on Internal Revenue Service documents for the last available fiscal year (1995). **Results** Estimated pharmaceutical advertising revenue ranged from $715,000 to $18,630,000. Five organizations raised more than 10% of their gross income (range 2% to 30%) from a single journal's pharmaceutical advertising. Four organizations raised as much or more from pharmaceutical advertising as from members (range 17% to 790%). **Conclusions** Potential financial conflicts of interest arising from pharmaceutical advertisements in medical journals may be substantial. The impact on professional societies' financial independence and behavior is unknown.

It is well documented that corporate contributions, usually in the form of gifts and favors, can affect clinicians' behavior.[1-8] In response to these findings, both the American Medical Association[9] and the American College of Physicians[10,11] have issued guidelines for recognizing and avoiding conflicts of interest, defined as "conditions that would cause reasonable persons (patients, colleagues, and citizens) to believe that professional judgment has been improperly influenced, whether or not it has."[12]

While guidelines on avoiding conflicts of interest exist for individual physicians, the same does not hold true for nonprofit physician organizations. On the contrary, many professional medical societies readily accept corporate contributions through continuing medical education funds, annual meeting support and fees, and academic and research grants.[11,13-16] While such funding clearly helps the underlying fiscal health of physician organizations, it also creates the same ethical conundrum for organizations as it does for individual physicians.[17,18]

A potential conflict also occurs because of pharmaceutical advertisements in medical journals. Such advertising helps to offset publishing costs but may also provide substantial operating funds for parent organizations,[19] thus creating potential conflicts of interest between professional medical societies and the pharmaceutical industry. While debate about pharmaceutical advertising has focused on its anecdotal value[19-24] or informational content,[25-30] little is known about the larger issue of potential conflicts of interest arising from the generated revenue. This study attempts to address this issue by estimating annual pharmaceutical advertising revenues for selected nonprofit physician organizations.

METHODS

Physician organizations and journal selection

We evaluated a convenience sample of six nonprofit physician organizations. Each organization owned and published at least one peer-reviewed journal that was of interest to internal medicine practitioners (generalists or specialists) and that allowed pharmaceutical advertising. The organizations were (in alphabetical order) American College of Cardiology, American College of Physicians, American Medical Association, American Thoracic Society (the medical section of the American Lung Association), Infectious Disease Society of America, and the Massachusetts Medical Society.

For each organization, we evaluated one primary clinical journal. The journals, listed in order of the organizations above, were Journal of the American College of Cardiology, Annals of Internal Medicine, Journal of the American Medical Association (JAMA), American Journal of Respiratory and Critical Care Medicine, Clinical Infectious Diseases, and The New England Journal of Medicine (NEJM).

Quantifying pharmaceutical advertising

To account for monthly variations in advertising budgets, we randomly selected 4 months (January, June, July, and November) in calendar year 1996 to evaluate pharmaceutical advertising. All journal editions published during those months were included. We did not evaluate supplements or newsletters.

We defined pharmaceutical advertisements as those advertisements for diagnostic or therapeutic, prescription or over-the-counter medications. Vaccines and nonpharmaceutical advertisements, such as those detailing devices and medical/surgical supplies, were not included. For each journal edition in the months selected, we tabulated the number of pharmaceutical advertisements, as defined above, and the total number of pages for those advertisements. Individual pages were then classified as primarily black & white or color. The average numbers of pharmaceutical advertisements and of advertising pages (black & white and color) for those medications were then estimated per edition.

For Annals of Internal Medicine, Journal of the American College of Cardiology, American Journal of Respiratory and Critical Care Medicine, and Clinical Infectious Diseases, the advertising in library editions was similar to editions received by practicing physicians. For these journals, our study used publications from the West Los Angeles Veterans Affairs (VA) Medical Center's medical library.

Two journals, NEJM and JAMA, produced multiple editions of their journals (same text but different pharmaceutical advertisements), with editions usually varying by geographic region and physician specialty. We were informed by publishing staffs that primary care physicians received editions with the most advertisements and libraries with the fewest advertisements. For these journals, we calculated the average number of pharmaceutical advertisements and of pharmaceutical advertising pages from the library edition (i.e., containing the lowest number of advertisements) and from a local (Los Angeles) primary care edition (i.e., containing the greatest number of advertisements). One primary care edition of the NEJM (4 January 1996) could not be procured. Therefore, to estimate the number of primary care pharmaceutical advertisements and advertising pages for that one issue, we used a multiplier based on the average difference in advertising between the library and the primary care versions.

Pharmaceutical advertising revenue

To calculate advertising revenue per edition, we used the published advertising rates for full-page black & white and color advertisements, then multiplied these by the average number of black & white and color advertisements per edition, as determined above. All advertising rates were obtained from the publisher in mid 1997.

Because we did not have access to publishers' commercial practices, we used assumptions designed to understate revenue. First, we rounded down the number of advertising pages to the nearest whole page. Second, pages with nominal color were categorized as black & and white, the least expensive classification. Third, we used the most common, and usually the mid-range cost, for color printing, known as "3- or 4-color process." Fourth, we used the earned discount rate (the discount for frequent advertising) for half the number of journal issues per year. So, if a journal put out 12 editions a year, we used the discount rate for 6 months of advertising. Fifth, advertising rates in special positions (inside front cover and inside back cover, for example) were calculated using the same rates as other pages. Sixth, to account for inflation from 1996 to 1997, we applied a 5% discount rate to advertising revenue.

Annual revenue was calculated by multiplying average advertising revenue per edition by the number of editions published per year. Revenues were adjusted for JAMA and NEJM by averaging the estimated revenue derived from primary care editions (with the highest number of advertisements) and library editions (with the base number of advertisements).

Conflict-of-interest measures

We focused on relative, rather than absolute, measures of financial support to better describe the proportional income effect on organizations, as had been suggested in previous literature.[12] We compared advertising revenue relative to an organization's total income to assess the level of financial risk faced by an organization, should that income be lost.[12] To compare advertising income to a primary internal revenue source, we compared pharmaceutical advertising revenue with an organization's membership dues and assessments.

To standardize organizational revenues, for each organization we used publicly available Department of Treasury Internal Revenue Service (IRS) Form 990, Return of Organization Exempt from Income Tax, for the last available fiscal year (1995). These documents were requested under Internal Revenue Code 6104 (IRC-6104). Organizations' fiscal years generally began and ended at midyear, although this was not always the case. Total revenue and membership dues and assessments were taken directly from line 12 and line 3, respectively, in Part I of Form 990.

RESULTS

The average number (standard deviation) of pharmaceutical advertisements per issue in the selected journals ranged from an average of 9.25 (4.4) in Clinical Infectious Diseases to 27.4 (5.4) in JAMA (primary care version) (see Table 1). The total number of pages of pharmaceutical advertisements was lowest in American Journal of

Table 1 *Pharmaceutical advertising in selected journals*

Organization Journal	ACC JACC	ACP Annals	AMA JAMA*	ATS AJRCCM	IDSA CID	MMS NEJM
Number of pharmaceutical advertisements per issue: average (SD)†	20.75 (5.0)	19.0 (4.6)	27.4 (5.4)	11.5 (3.5)	9.25 (4.4)	21.875 (2.6)
Total pages of pharmaceutical advertising per issue: average (SD)	99.0 (18.4)	61.5 (13.2)	71.7 (16.4)	27.25 (12.0)	27.5 (11.5)	60.6 (9.4)
Text pages per issue: average (SD)	294.25 (42.1)	81.25 (5.6)	78.7 (7.7)	353.5 (90.6)	232.5 (24.1)	70.9 (7.6)
Ratio of pharmaceutical advertising pages to text pages	0.34	0.76	0.91	0.08	0.12	0.85
Estimated revenue from pharmaceutical advertising per issue	$359,420	$250,123	$372,572	$59,790	$59,614	$275,211
Estimated gross revenue from pharmaceutical advertising (millions/year)	$4.67	$6.00	$18.63	$0.717	$0.715	$14.31
Pharmaceutical advertising revenue as a proportion of total revenue (%)	13.8	12.9	10.4	2.1	31.3	21.3
Pharmaceutical advertising revenue as a proportion of membership dues and assessments (%)	93.0	133.9	26.2	17.1	125.4	792.7

ACC = American College of Cardiology (JACC = Journal of the American College of Cardiology); ACP = American College of Physicians (Annals = Annals of Internal Medicine); AMA = American Medical Association (JAMA = Journal of the American Medical Association); ATS = American Thoracic Society (AJRCCM = American Journal of Respiratory and Critical Care Medicine); IDSA = Infectious Disease Society of America (CID = Clinical Infectious Diseases); MMS = Massachusetts Medical Society (NEJM = The New England Journal of Medicine).
*Data presented for JAMA and NEJM are based on primary care edition except for advertising revenues, which were calculated from the average of primary care and library editions (see text for details).
†SD = standard deviation.

Respiratory and Critical Care Medicine (27.25 [12.0]) and highest in Journal of the American College of Cardiology (99 [18.4]) (Table 1). The proportion of black & white pages to color pages ranged from approximately 63% to 79% (data not shown). The ratio of pharmaceutical advertising pages to text pages (Table 1), which included editorials, book reviews, and letters, was lowest for the American Journal of Respiratory and Critical Care Medicine (0.8) and Clinical Infectious Diseases (11.12) and highest for the primary care versions of JAMA (0.91) and NEJM (0.85). The primary care version of JAMA contained about three times more advertisements than the library copy, whereas the primary care version of NEJM contained slightly less than 1 1/3 more (data not shown).

Our estimates indicated that pharmaceutical advertising raised nearly $46 million in calendar year 1996 for the six selected journals. There was a wide range of advertising revenues ($715,000 to $18,630,000), but these did not necessarily correspond to proportional measures of financial support (Table 1). For example, pharmaceutical advertising revenue from Clinical Infectious Diseases was fairly small (about $715,000) but represented nearly 30% of the gross revenue for the Infectious Disease Society of America. On the other hand, with nearly the same total ($717,000), the American Thoracic Society had the lowest proportional support at approximately 2% of total revenue. Overall, five of the six organizations raised 10% or more of their total annual revenue from a single journal's advertising (Table 1).

Four organizations generated as much or nearly as much revenue from pharmaceutical advertisements as from membership dues and other assessments. For example, advertising revenue from NEJM brought in almost eight times more money than did member contributions to the Massachusetts Medical Society. Conversely, the advertising revenue for the American Thoracic Society amounted to less than a fifth of membership dues and assessments (Table 1).

DISCUSSION

Our estimates suggest that nonprofit physician organizations may have substantial potential conflicts of interest due to pharmaceutical advertising revenues, even from a single journal. As Blumenthal pointed out, conflicts of interest are conditions, not behaviors,[31] so our results should not imply that pharmaceutical firms have influence over physician organizations (or their journals) due to advertising. Further, the data for each organization was

generated from a single journal, not from all publications. There were disparities among organizations and journals as well. For example, the Massachusetts Medical Society is a relatively small medical society, but NEJM has an international audience; we would expect it to have a greater disproportion between membership dues and pharmaceutical advertising revenue than other professional societies.

Some may argue that the potential conflict of interest is only at the level of the journal and that editorial independence eliminates it.[19] Another argument is that profits are small because the advertising income is used to support editorial staff and publishing costs. These arguments are not accurate, however, because a journal is ultimately the responsibility of its parent organization, as was shown by recent events at JAMA,[32] and because advertising revenue allows organizations to shift other revenue streams (membership dues and assessments and various user fees, for example) to alternative purposes or to enhance gross income. For example, five of the six organizations examined had surpluses in fiscal year 1995.

The concerns that individual physicians will alter prescribing behavior because of interactions with or gifts from pharmaceutical representatives is not applicable to professional medical societies.[1-6,8,10,11] Nonetheless, the money from advertising helps support organizations in their public and educational missions and in their membership advocacy. As Ubel and colleagues pointed out, since nonprofit organizations can become dependent on financial support, an organization may become reliant on external funds, compromising itself to attract or maintain desired revenue levels.[18]

The likelihood of dependency increases as the proportion of income from a single source increases relative to gross income.[18] Similar to individuals, an organization under considerable financial risk is more likely to have, or to be perceived as having, a serious potential conflict of interest. For individuals, the Health Care Financing Administration defines "substantial financial risk" as a potential withholding (e.g., possible gain or loss) of more than 25% of expected earnings.[33] By our estimates, only one physician organization reached that level of financial risk from pharmaceutical advertising with a single journal, but our study could not include revenue derived from all financial interactions with the pharmaceutical industry. Yet even if the sum were less than 25%, we would be concerned because it is unclear what threshold of financial risk qualifies as a conflict of interest for a nonprofit organization.[34]

On the other hand, it is unlikely that any single corporation buys enough advertising space to cause an organization to become dependent. This lessens the likelihood that any one corporation could influence a physician organization by threatening to withhold advertising. Nonetheless, as Pritchard pointed out in discussing institutional relations with industry, the cumulative effects of numerous small revenue streams should not be discounted.[34] Moreover, individual pharmaceutical firms have been known to take action against researchers when it is in the firms' best interest.[35] Further, collective corporate action is possible, as suggested by at least one commentator[30] discussing the downturn in pharmaceutical advertising in Annals of Internal Medicine[36] following publication of the 1992 article critical of drug advertisements by Wilkes and colleagues.[28]

Outside revenue can also compromise an organization by creating a sense of obligation to the revenue sources.[18] For several organizations, the money generated from a single journal's pharmaceutical advertising provided financial support equal to or greater than that brought in by members themselves. Consequences of such undue influence could include allowing advertisers greater access to physicians at annual meetings or having a high-ranking member lobby on behalf of advertisers.

Finally, potential financial conflicts of interest can damage an organization's credibility with both the public and policymakers.[37] Moreover, the damage to credibility can interfere with an organization's ability to act as a role model.[18] For example, we believe that any message admonishing physicians to avoid gifts and favors from the pharmaceutical industry appears contradictory when physician organizations benefit extensively from the same source.

It is important to discuss the limitations of this study. Because publishing staff uniformly rebuffed our queries about business matters, we felt it best to provide low-end estimates of drug advertising revenues. Still, our discounts may have been too small or too large. For example, in the case of JAMA, using 1 year instead of 6 months for the earned discount rate would have reduced revenues by about 2% overall. Using a less expensive printing process (i.e., 2-color process) to calculate revenues would have reduced advertising income by 15%, but most color advertisements appeared to use 3- or 4-color process. The year we chose to assess advertising may not be representative of other years. Some organizations do not own journals, and some journals are not wholly owned by organizations or are owned solely by private publishers.

The purpose of our study was not to censure organizations but to quantify potential conflicts of interest for nonprofit physician societies that generate revenue from corporate sources. We believe that it is important for medical societies to recognize that pharmaceutical advertising revenue can strongly affect their financial health. To minimize any adverse perceptions or effects associated with these potential financial conflicts of interest, we encourage nonprofit physician organizations to openly

disclose gross advertising revenue accruing from pharmaceutical advertising and, for that matter, gross revenue accruing from all financial interactions with the pharmaceutical industry.

Finally, in the absence of guidelines, we strongly encourage nonprofit physician organizations to consult annually with their members to decide democratically what threshold of subsidy is acceptable. As a guiding principle, and to echo the American College of Physicians, professional societies and their members should ask themselves, "What would the public or [our] patients think of this arrangement?"[11]

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COMMENTARY

Don't bite the hand that feeds you

"Don't bite the hand that feeds you" is a line from a 1971 song by a Canadian folk group, Humphrey and the Dumptrucks. And it is the issue posed by this article. Are medical organizations willing, if necessary, to bite the pharmaceutical industry hand that feeds them? Circumstantial evidence suggests that they may not be. Why did the American Medical Association (AMA) wait until a week before the Senate Labor and Human Resources Committee hearings on the promotional excesses of the pharmaceutical industry before they adopted ethical guidelines about travel expenses and gifts?[1] Was it the prospect of being embarrassed by their own previous inaction that prompted the AMA to act?

During the mid 1980s, the Canadian government commissioned an inquiry into whether compulsory licensing

for pharmaceuticals should be retained. (Under compulsory licensing, a company can be granted permission to market a drug that is still under patent in return for payment of a royalty to the patent holder. Compulsory licensing was vigorously opposed by the brand name industry.) In a 1984 brief responding to the inquiry, the Canadian Medical Association (CMA) echoed many of the positions taken by the Pharmaceutical Manufacturers Association of Canada (PMAC).[2] That same year, net revenue from the Canadian Medical Association Journal, mostly from pharmaceutical advertising, came to $537,203. Were it not for this income, the CMA would have suffered a loss of $661,570, instead of a loss of just under $125,000.[3]

There is growing concern about the relationship between the World Health Organization (WHO) and the pharmaceutical industry. In conjunction with the International Society of Hypertension, WHO recently issued a set of guidelines for the management of hypertension. A letter signed by close to 900 doctors and scientists pointed out that the guidelines ignored ground rules of clinical assessment and placed a great deal of weight on the results of two trials funded by pharmaceutical companies.[4] In addition, the letter pointed out that WHO has been accepting temporary substitutes of personnel from the pharmaceutical industry, bringing into question "how the WHO is currently working to avoid any actual or perceived conflict of interest when accepting funds from and working closely with commercial enterprises."[5]

When organizations have bitten industry's hand, there have been allegations of retaliation. The Canadian Medical Association Journal carried an article (1194;150(6):951-953) that discussed what happened when the internal medicine residency program at McMaster University adopted a set of formal guidelines for the interaction between residents and the pharmaceutical industry. Those guidelines prohibited residents from receiving noneducational benefits, including "drug lunches," and excluded industry representatives from residents' educational events. Shortly afterward, a senior official with PMAC visited the director of the McMaster residency program and suggested that industry funding for educational as well as research activities could be compromised by the guidelines. (In a formal letter, however, the president of PMAC denied any policy to withhold funding.)[6]

Circumstantial evidence and allegations don't make a case, but even the perception of conflict of interest is enough to damage the reputation of medical associations. Although associations represent the interests of their members, they should also advocate that patients get the highest-quality medical care. The main function of pharmaceutical companies is to give their shareholders the best possible return on their money. If the public believes that medical associations have adopted the value systems of private enterprise, then trust in physicians will slip another notch.

Concern about conflict of interest arising from drug company funding has spread to patient and consumer groups, who may provide some guidance on how to approach the issue.[7] Above all, organizations have to acknowledge openly and publicly the amount of money that advertising generates for the group. They need to be vigilant in ensuring that decisions about the priorities and policies of the organization are made in a public and democratic manner, so that accusations of bias can be countered.

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capsule

Are hernias and aneurysms related? Researchers from the Netherlands have found a link between inguinal hernias and abdominal aortic aneurysms in men (British Journal of Surgery 1999;86:1155-1158). Degeneration of collagen and elastin by overactive elastase and collagenase enzymes may be behind both diseases, they say, and suggest that men with hernias should be added to the list of potential targets for aneurysm screening, which currently includes smokers, people with hypertension, and relatives of people with abdominal aortic aneurysms.

Research Digest

Cognitive behavioral group therapy and phenelzine both effective in social phobia

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Arch Gen Psychiatry 1998;55:1133-1141.

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Question
In adults with social phobia, is cognitive behavioral group therapy (CBGT) effective as compared with phenelzine?

Design
Twelve-week randomized placebo-controlled trial

Setting
Two clinical centers for anxiety disorders in New York

Participants
A total of 133 patients were included in the trial aged 19 to 61 years (mean age 35 years, 50% women) and met criteria for social phobia in the Diagnostic and Statistical Manual of Mental Disorders. Exclusion criteria included schizophrenia, major depression, prominent risk of self-harm, organic mental disorder, history of bipolar I disorder, substance abuse in the previous 6 months, previous adequate trial of cognitive behavioral therapy, or use of monoamine oxidase inhibitors for social phobia and serious medical conditions. Follow-up was 80%.

Intervention
After being stratified by social phobia subtype, patients were allocated to three treatment groups: those receiving phenelzine sulfate, 15 mg (n=31); those receiving matching placebo (n=33); those receiving CBGT (n=36); and those receiving educational and supportive group therapy (attention placebo procedure; n=33). Phenelzine doses were started at 15 mg/day and increased to 30 mg/day on day 4, to 45 mg/day on day 8, and to 60 mg/day on day 15. Doses could be raised to 75 mg/day after 4 weeks and to 90 mg/day after 5 weeks. CBGT consisted of 12 sessions of 2.5 hours with five to seven patients in each group; patients were encouraged to identify and counteract negative thoughts, to confront fearful situations, and to meet behavioral goals. The attention placebo procedure included supportive group therapy and presentation and discussion of topics relevant to social phobia.

Main outcome measure
Response was assessed with the Social Phobic Disorders Severity and Change Form (score of 1 or 2).

Main results
Analysis was by intention to treat. At 12 weeks, rates of response were 58% for CBGT, 65% for phenelzine, 33% for placebo, and 27% for attention placebo procedure. More patients responded to CBGT and phenelzine than in the respective placebo groups (P<0.005); the response rate did not differ between CBGT and phenelzine (see Table 1).

Conclusion
In patients with social phobia, cognitive behavioral group therapy and phenelzine were both effective.

Table 1 *Response rate for treatment of social phobia at 12 weeks. Values are percentages.*

Comparisons	Experimental event rate	Control event rate	Relative benefit increase (95% CI)*	Number needed to treat (CI)*
Cognitive behavioral group therapy vs attention placebo	58	27	114 (19 to 307)	4 (2 to 14)
Phenelzine vs placebo	65	33	94 (15 to 243)	4 (2 to 16)
Phenelzine vs cognitive behavioral group therapy	65	58	11 (−25 to 63)	NS

NS=not significant.
*Calculated from data in article.

COMMENTARY
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Apart from the competent appraisal of treatment effects themselves, the authors examined whether disparate outcomes were associated with the two service settings. Fortunately, allegiance effects seemed nonexistent; CBGT and phenelzine were equivalently effective regardless of site. The use of credible placebo control groups for CBGT and phenelzine enhances the validity of the conclusion that the two primary therapies being tested were genuinely effective in alleviating social phobia.

The authors are to be commended for including estimates of the magnitude of effect size for selected outcome measures.[1] Another useful outcome measure, which was not included in this study, is the numbers of patients in each group who no longer meet the DSM criteria for social phobia at the conclusion of treatment, which is truly the acid test of any therapy.

Both phenelzine and CBGT are apparently effective in the short term (after 12 weeks of treatment). What will be of equal interest is what happens to patients at long-term follow-up once active therapies are stopped. Are behavioral competencies acquired during CBGT maintained and generalized once group therapy is concluded? What happens to phobic anxiety when phenelzine is withdrawn? For some anxiety disorders, selected psychotropic medications are a good treatment but a bad cure, with high relapse rates once drugs are stopped.

The same disorders treated behaviorally show slower initial improvements but more durable positive effects once treatment is stopped. Will the same pattern emerge for social phobia? On the basis of this and related clinical trials, clinicians should consider either CBGT or phenelzine as best practices in caring for patients with social phobia.

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Befriending can lead to remission in women with chronic depression

Question
Does befriending by volunteers improve symptoms and increase the frequency of recovery in women with chronic depression?

Design
Randomized unblinded controlled trial with follow-up to 1 year

Setting
Inner-city London

Participants
A total of 86 patients (age concentration 25 to 40 years) were recruited through a postal screening of all women registered with certain general practices in Islington, London. The clinical interview to determine whether chronic depression reached case level used an abbreviated form of the Present State Examination (PSE-10). Four out of 10 core symptoms had to be present, along with depressed mood. Exclusion criteria were severe comorbid conditions of substance misuse or eating disorders or lack of interest in the provisional offer of befriending.

Intervention
Forty-three participants were assigned to befriending and 43 to a waiting list control group. Volunteers to befriend the participants were recruited through advertisements, were interviewed and trained by social workers, and were matched to the 43 women in the befriending group. Befriending was defined as meeting and talking with the woman who was depressed for a minimum of 1 hour each week and acting as a "friend" to her—listening and "being there" for her.

Main outcome measure
Overall remission (minimum 2 months and including partial remission) based on the PSE-10.

Main results
Analysis was by intention to treat. Overall remission occurred more frequently in women in the befriending group than in the control group (P=0.02)* (see Table 1). Altogether, 18 of 43 women (42%) allocated to the befriending group met with their volunteer only once or not at all. Ten of these 18 women went into remission. Although the frequency of remission tended to be higher among those receiving the full 12 months of befriending as compared with those receiving 2 to 6 months (76% [13 of 17 patients] vs 63% [5 of 8 patients]), this difference did not reach statistical significance.

Table 1 *Befriending versus waiting list control in women with chronic depression. Values are percentages unless indicated otherwise.*

Outcome at 1 year	Befriending	Waiting list control	Relative benefit increase (95% CI)*	Number needed to treat (CI)*
Overall remission	65	40	65 (9 to 158	4 (3 to 23)

*Calculated from data in article.

Conclusion
Befriending led to a higher frequency of overall remission in women with chronic depression.

COMMENTARY
Robert Peveler, University of Southampton, United Kingdom

There is a considerable choice of treatment modalities of proven efficacy for treating depression, including cognitive therapy, interpersonal psychotherapy, and drug treatments. We have also witnessed an explosion of counseling, an intervention with a much more slender evidence base. Is befriending as effective as other proven treatments?

The size of the benefit for treated women who agreed to enter the trial suggests that it is of the same order of magnitude as for other proven treatments, with a number needed to treat of about four. In a companion paper, the possible mechanisms of action of the intervention are explored.[1] The conclusion of this investigation is that attachment style, positive and negative life events during the year of study, and, especially, "fresh-start events" seem to be important predictors of remission.

Psychosocial treatments are vulnerable to accusations of high cost. In this case, however, treatment was provided by volunteers, so the only direct healthcare costs were those of training.

Although based on a community sample, patients in the present study resemble a secondary-care population because they have been extensively filtered to select only those women whose depressive disorder has been present for at least 1 year. Of greatest concern is that only about one in three of the suitable participants agreed to be allocated to the befriending treatment. Commentators often remark on the low acceptability of drug treatments to patients, but a refusal rate of almost two thirds severely limits the generalizability of the findings, especially in an unblinded trial.

Before the results influence the practice of mental healthcare teams, replication in another center is desirable.

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How do Oregon psychologists view their role in physician-assisted suicide?

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Question

How do Oregon psychologists view physician-assisted suicide and their role in the process of assessing patients who request such assistance, and do personal attitudes influence professional viewpoints?

Design

Mailed questionnaire

Setting

Oregon

Participants

Of the 846 licensed psychologists in Oregon, 625 were randomly selected by computerized random-number assignment to receive the questionnaire. There was a return rate of 74%, of which 38 were excluded because the respondents were not in active clinical practice. There were 423 final participants, 50% of all Oregon psychologists. The mean age was 48.8±8.1 years (range 31 to 76 years), 57% were male, and 95% had doctoral degrees (PhD, PsyD, or EdD).

Methods

The anonymous questionnaire contained both closed-choice and open-ended items that covered issues concerning physician-assisted suicide mentioned in the scientific literature, lay press, and collegial discussions. The survey assessed personal views about physician-assisted suicide, the Oregon Death with Dignity Act (ODDA), the ODDA mental health safeguard, and the role of the psychologist in the ODDA.

Main findings

Most respondents (78%) favored the ODDA, and most (67%) considered the mental health safeguard adequate. But there was an association between a positive view of the safeguard and general support for the ODDA ($P<0.001$). Of the 275 psychologists surveyed who indicated performing an evaluation under the ODDA would be within their scope of practice, only 60% indicated that they would perform the evaluation. When placed in the context of a single evaluation, 50% of respondents replied that they were "not at all confident" in the results of their evaluation, with only 7% indicating that they were "very confident." Overall, 62% reported that they would provide the assessment to the referring physician and then take no further action; 28% would support the patient through the rest of the process; and 10% would work with the patient to prevent the suicide. The perceived role of the psychologist and confidence in the evaluation correlated with support or opposition of the ODDA, such that those opposed were more likely to see their role as working to prevent the suicide ($P<0.001$) and felt more uncomfortable with the validity of an assessment after a single evaluation ($P<0.05$).

COMMENTARY

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The ODDA legalizes physician-assisted suicide for competent, terminally ill patients who request it. One safeguard built into the law states that if a physician suspects psychiatric or psychological disease that can impair judgment, such as depression, then a mental health assessment must be performed. If the assessment reveals a mental disorder that impairs judgment, then no lethal medication can be prescribed. Hence the mental health evaluations of patients requesting assisted suicide carry mortal importance.

This survey of a random sample of Oregon psychologists was a companion to a similar survey of Oregon psychiatrists presented elsewhere.[1] The results were parallel. Despite their role in suicide prevention, most of these psychologists endorsed the ODDA. The assumption of the safeguard is that the mental health evaluation will be an objective assessment, but like the rest of the health profession and Americans, psychologists are divided in their attitudes and moral framework. The weight of the various factors in support or opposition of assisted suicide—like patient suffering, self-determination, and moral contention—varied markedly and was largely based on personal values and judgment. Psychologists' positions on legalization of assisted suicide influenced their perception of their roles in the assessment process and their confidence in assessing patients adequately.

This study suggests that these attitudes will influence the role that the psychologist plays in a person's request for assisted suicide and, potentially, the assessment. The study took place during a period of polarized public debate over assisted suicide.

What happens in Oregon will likely set the standards of practice and intervention by mental health professionals, as other states consider similar legislation. The debate and subsequent practice must resolve whether assisted suicide is different enough from suicide that mental health professionals can deviate from their primary mission of preventing suicide, whether it is possible for the mental health safeguard to be a neutral evaluation, and whether it should be so. If this cannot be resolved, then we must reconsider the value of the safeguard and who should be eligible to assess the mental health of these patients. Now that we have a year's experience with the ODDA in Oregon, it would be enlightening to hear from the participating mental health professionals.[2]

1 Ganzinei L, Fenn DS, Lee MA, et al. Attitudes of Oregon psychiatrists toward physician-assisted suicide. Am J Psychiatry 1996;153:1469-1475.

2 Chin AE, Hedberg K, Higginson GK, Fleming DW. Legalized physician-assisted suicide in Oregon: the first year's experience. N Engl J Med 1999;340:577-583.

Best Practice

EVIDENCE-BASED CASE REVIEW

Osteoma cutis (cutaneous ossification)

Objectives

- Understand the possible systemic significance of cutaneous calcification and ossification
- Learn the clinical classification of osteoma cutis and calcinosis cutis
- Understand the diagnostic work-up
- Recognize the treatment options

Cutaneous calcification and ossification both involve the deposition of calcium salts in cutaneous and subcutaneous tissues. Derangements of calcium metabolism can sometimes cause cutaneous calcification or ossification as a first sign of systemic disease. Both processes (referred to in the dermatology literature as calcinosis cutis and osteoma cutis) are rare, with only scattered cases reported in the literature. Cutaneous calcification (calcinosis cutis) is traditionally divided into four broad categories: metastatic, dystrophic, iatrogenic, and idiopathic (Table 1).[1]

Metastatic cutaneous calcification is calcium deposition due to a disorder of calcium or phosphorus homeostasis and is usually associated with elevated serum calcium or phosphate levels. Dystrophic calcification is calcification that develops as part of a preexisting pathologic skin process such as a tumor. This form of cutaneous calcification shows no elevations of serum calcium or phosphate values. Cutaneous ossification (osteoma cutis) is likewise divided into categories, referred to as primary and secondary osteoma cutis.

Osteoma cutis

I. Primary
- a) Albright's hereditary osteodystrophy
- b) Not associated with Albright's hereditary osteodystrophy
  - i) Multiple miliary osteomas of the face
  - ii) Isolated osteoma
  - iii) Widespread osteoma
  - iv) Congenital plaque-like osteoma

II. Secondary
- a) Inflammatory skin disease
  - i) Progressive systemic sclerosis and CREST syndrome
  - ii) Dermatomyositis
  - iii) Morphea
- b) Tumors/Neoplasms
  - i) Basal cell carcinoma, pilomatricoma, etc.
- c) Trauma and scars

Secondary osteomas account for 85% of cutaneous ossifications and develop within preexisting neoplastic or inflammatory skin lesions. Primary osteoma cutis accounts for about 15% of cutaneous ossifications and develops on its own (see box above).[2]

Information on the topics discussed in this review and following case history was obtained through a literature search using PubMed and the following key words: cutaneous ossification,[1,3] osteoma cutis,[2,4,5] and calcinosis.[6] A 4-mm punch biopsy was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. Sections were examined using light microscopy. Clinical data were obtained through direct interview with the patient as well as review of laboratory and radiograph records.

Case history

A 66-year-old African-American woman with a history of coronary artery disease, congestive heart failure, diabetes, and hypertension presented with incidental findings of multiple firm, nontender, subcutaneous plaques and nodules involving the lateral aspect of the right and left thighs, extending to the knees (Figure 1). The nodules had been present for 30 years, recently increasing in number after a myocardial infarction. At times she had also suffered from painful extrusions of "chalky bone." The patient denied any history of trauma, inflammatory changes, nevi, or other dermatologic conditions. She had no other significant medical conditions and no family history of similar skin lesions.

Laboratory studies showed an elevated erythrocyte sedimentation rate of 114 mm/hour, a random glucose of 157 mg/dl, a mildly depressed total serum iron and iron saturation (27 ug/dl and 10%, respectively), and mildly elevated blood urea and nitrogen (28 mg/dl) and creatinine (1.6 mg/dl). The rest of the laboratory results, including electrolytes, serum calcium, phosphate, alkaline phosphatase, and angiotensin-converting enzyme levels, were within normal limits.

Her chest X ray showed a prominent right hilum with calcified lymph nodes. Venous Doppler examination of lower extremities, to rule out deep venous thrombosis, was technically difficult because of severe calcium deposits. A 4-mm punch biopsy obtained from the right leg showed variably sized spicules of mature lamellar bone within the subcutaneous fat (Figure 2).

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Table 1 *Some causes of dermatologic calcifications*[7]

Dystrophic	Metastatic	Idiopathic	Iatrogenic
Progressive systemic sclerosis	Chronic renal failure	Subepidermal calcified nodules	I.V. calcium chloride/ gluconate therapy
CREST syndrome	Sarcoidosis	Idiopathic calcification of the scrotum	
Panniculitis	Albright's hereditary osteodystrophy	Tumoral calcinosis	
Ehlers-Danlos	Neoplasms	Progressive osseous heteroplasia	
Cutaneous neoplasm	Pseudohyper-parathyroidism		
Trauma			
Infection			

What medical conditions are associated with cutaneous ossification and cutaneous calcification?

Cutaneous ossification (osteoma cutis) can be divided into primary and secondary osteoma cutis, both of which are quite rare. Primary osteoma cutis is divided into two subclasses. The first is associated with Albright's hereditary osteodystrophy, which has poor long-term prognosis. Two syndromes are included in Albright's hereditary osteodystrophy: pseudohypoparathyroidism and pseudopseudohypoparathyroidism. The characteristic features of both syndromes include obesity, developmental disability, short stature, round facies, basal ganglia calcification, and osteoma cutis.[2,3] Patients with pseudohypoparathyroidism have end-organ resistance to the action of parathyroid hormone and have hypocalcemica/hyperphosphatemia, despite high levels of parathyroid hormone. Patients who have pseudopseudohypoparathyroidism are similar phenotypically except that the results of their laboratory tests are within normal limits.

Patients with the subclass of primary osteoma cutis that is not associated with Albright's hereditary osteodystrophy have a good long-term prognosis. The subclass is further divided: multiple miliary osteoma of the face, isolated osteoma, widespread osteoma, and congenital plaque-like osteoma.[3] Multiple miliary osteoma is restricted to the face and usually occurs in women. Isolated osteoma can occur at any cutaneous site and presents as a single isolated nodule. Widespread osteoma presents in the neonatal period as multiple generalized subcutaneous osteomas. Likewise, congenital plaque-like osteoma occurs in the neonatal period but morphologically presents as a large plaque on the extremities or the scalp.

Secondary osteoma cutis is quite rare, but relatively more common than the primary form, accounting for 85% of all cutaneous ossifications. By definition, secondary osteoma cutis occurs in association with antecedent skin inflammation, injury, or tumor[4] (box). Some of the clinically significant lesions include neoplasms (metastatic bronchogenic carcinoma, basal cell carcinoma, Gardner's syndrome, hemangioma), inflammatory skin disease (syphilis, pyogenic granuloma, folliculitis), and collagen vascular disease (CREST syndrome, dermatomyositis, lupus erythematosus).[4] Hence a thorough diagnostic work-up is important, because cutaneous ossification is not just a sign of present systemic disease, it may even precede it.

Cutaneous calcification (calcinosis cutis) and osteoma cutis overlap in terms of their pathogenesis and associated conditions (Table 1). Dystrophic calcification, the most common form of calcinosis cutis, does not alter patients' levels of serum calcium or phosphorus, but it shares many of the same underlying conditions with secondary osteoma cutis. Dystrophic calcinosis cutis can result from neoplasms, granulomatous conditions, collagen vascular disease (in particular CREST syndrome), systemic lupus erythematosus, and childhood dermatomyositis.

On the other hand, metastatic calcification is that form of calcification that results from increased serum calcium or phosphate levels. Multi-organ involvement of kidney, lungs, and arteries is common, but at times metastatic calcification can present as calcinosis cutis. Cutaneous lesions are most commonly seen in patients with chronic renal failure and are thought to be due to poor phosphate clearance. In this clinical setting, nodules of calcinosis cutis have a periarticular distribution and usually resolve when patients' levels of serum calcium and phosphorus return to normal. Metastatic cal-

Figure 1 *Bilateral multiple hard subcutaneous nodules and plaques are present on the lateral thighs of this 66-year-old woman.*

cinosis cutis has also been reported in association with AIDS, lymphomas, pseudohyperparathyroidism, and sarcoidosis.

What is the diagnostic approach?

This case is somewhat difficult to classify. The extent of ossification in this patient prompted us to look for a systemic disease, particularly one that might alter calcium and phosphorus homeostasis, but the patient's levels of serum calcium and phosphate were normal. The fact that the patient developed the lesions near the age of 35 years ruled out many of the congenital and neonatal primary cutaneous ossifications. The patient also did not have phenotypic features of Albright's hereditary osteodystrophy or the hypocalcemia/hyperphosphatemia associated with pseudohypoparathyroidism. The absence of a secondary process within the biopsy ruled out secondary cutaneous ossification, as occurs in tumors, nevi, or other inflammatory conditions, and the patient had no clinical signs to suggest a collagen vascular disorder, such as progressive systemic sclerosis. Also in the differential diagnosis was cutaneous calcification and its associated conditions (Table 1), ruled out by a combination of history, laboratory data, and, most importantly, biopsy appearances. Histopathologically, calcinosis cutis demonstrates masses of basophilic material, usually surrounded by a chronic granulomatous foreign body-type inflammatory reaction. In contrast, osteoma cutis demonstrates either basophilic or eosinophilic deposits arranged in the form of spicules. In contrast to calcinosis cutis, osteoma cutis demonstrates the characteristic lamellar arrangement of mature bone when viewed via polarization microscopy.

A rare form of secondary cutaneous ossification occurs in association with chronic venous insufficiency and preferentially affects the lower extremities; in most patients, however, the cutaneous osteomas are localized to the lower leg, not the upper leg, as in this patient.[7] Furthermore, this patient had no obvious clinical symptoms or signs of venous insufficiency.

In summary, this patient presents an unusual form of cutaneous ossification restricted to the bilateral thighs. Because there is no apparent associated dermatologic condition, we consider it a form of idiopathic non-Albright's hereditary osteodystrophy primary osteoma cutis, which aside from its cosmetic deformity is of no serious clinical consequence.

What are possible pathogenic mechanisms for osteoma cutis?

The mechanism of cutaneous ossification is unclear, but most theoretical speculations suggest that the bone deposition is due to the ability of either resident fibroblasts or nests of pleuripotent mesenchymal cells to differentiate into osteoblasts.[5]

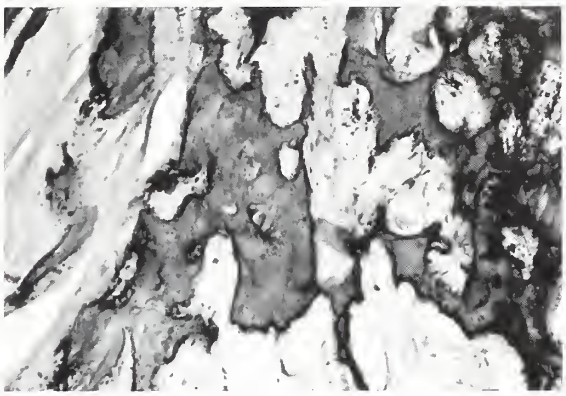

Figure 2 *Within the deep dermis and subcutaneous fat are multiple spicules of mature lamellar bone.*

What are the treatment possibilities?

The treatment of underlying disease is the first step. Various medical and surgical therapies have been tried for individual lesions of osteoma cutis. Unfortunately, synthetic diphosphonates, such as etidronate disodium, do not seem to be effective in treatment. Surgical excision, including punch excisions, are currently the treatment of choice for osteoma cutis, if the patient is symptomatic. Ultrasound studies may aid in surgical planning by localizing small and deeper lesions.[8]

Like osteoma cutis, the treatment of calcinosis cutis has met with varied success.[4] In general, diphosphonates and steroids have also not been successful. Diltiazem treatment has been reported to cause dramatic calcinosis regression in systemic scleroderma. There have been similar reports of success with diltiazem use in juvenile dermatomyositis.[6] One theory behind the action of diltiazem is that it prevents calcium influx into the calcifying tissue and that this is followed by macrophage clearance of the lesion.[4] Surgical treatment is also an option for cutaneous calcification, particularly in cases of physical impairment, recurrent ulcerations, unremitting painful lesions, or cosmetic deformity.

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CLINICAL EVIDENCE

Emerging approaches in preventing cardiovascular disease

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Summary points

- Classical risk factors for atherosclerosis cannot fully explain why certain people develop coronary heart disease and stroke and others do not.
- Other potential ("emerging") risk factors for atherosclerosis and new preventive treatments are currently being studied.
- Promising new preventive treatments include antioxidants, lowering of homocysteine concentrations, decreasing the activation of the renin-angiotensin system and the coagulation system, antibiotics, and anti-inflammatory agents.
- The efficacy of these treatments has not been proven in clinical trials; at present, the emphasis should be on treating established risk factors and consistently applying treatments that are known to reduce cardiovascular morbidity and mortality.

Reducing cholesterol and blood pressure, as well as smoking cessation, have been shown to be effective strategies for preventing cardiovascular diseases.[1] These "classical" risk factors, however, along with known nonmodifiable risk factors such as age, sex, and family history, cannot fully explain why some people develop myocardial infarction and stroke and others do not.[2-4] Additional factors may have a role in the pathogenesis of atherosclerosis, and new preventive strategies may be of use. In this article, we briefly review the use of antioxidants, the use of angiotensin-converting enzyme inhibitors, and homocysteine lowering. Other "emerging" cardiovascular risk factors and potential preventive strategies that are under investigation are summarized in Table 1.

OXIDATIVE STRESS AND ANTIOXIDANTS

Extensive laboratory data show that oxidative modification of low-density lipoprotein (LDL) cholesterol is an important step in the pathogenesis of atherosclerosis, and experimental studies in different animal models show that antioxidants decrease oxidation of LDL cholesterol and reduce the formation of plaques.[5,6]

Epidemiological studies have generally reported that an increased intake of antioxidants through diet or supplements, particularly vitamins E and C and β-carotene, is associated with a lower risk of coronary heart disease.[7-9] Other antioxidants, such as other carotenoids, flavonoids, selenium, magnesium, and monounsaturated fat, are also found in natural food products and may reduce oxidation of LDL cholesterol. The most compelling results have been with vitamin E supplementation.[10-12] These epidemiological studies have several methodological limitations, however. Although most observational studies have attempted to adjust statistically for other factors that could affect the cardiovascular risk, such adjustments are difficult and not always adequate. Lifestyle and dietary patterns not accounted for could contribute to some of the observed, apparent, lower cardiovascular risk in people who use supplemental vitamins in comparison to nonusers, and similar confounders could bias the results of epidemiological studies evaluating dietary intake of antioxidant vitamins. Therefore the role of specific vitamins in the prevention of coronary heart disease is best evaluated in randomized clinical trials.

Trials of vitamin E

Three large randomized placebo-controlled trials of vitamin E have been completed (Table 2). The α-Tocopherol β-Carotene Cancer Prevention Study (ATBC) was designed primarily to assess the effects of daily supplementation with α-tocopherol and β-carotene on cancer.[13] A total of 29,133 Finnish male smokers were randomly assigned to treatment with α-tocopherol (vitamin E) 50 mg daily or placebo and β-carotene 20 mg daily or placebo for 5 to 7 years. Vitamin E did not prevent death from cardiovascular disease or myocardial infarction. The incidence of angina pectoris was modestly reduced (relative risk reduction = 9%, 95% confidence interval 1% to17%; P=0.04).[14] In the subgroup of individuals with previous myocardial infarction, modest benefits on nonfatal coronary events were reported, but there was no effect on cardiac mortality.[15] The major limitation of this trial was the vitamin E dose used (50 mg/day), which is much lower than the doses suggested by most of the epidemiological data to be cardioprotective.

A second large primary prevention trial conducted in China reported a marginally significant reduction in total mortality (9%, 0% to 70%) for a combination of vitamin E, β-carotene, and selenium, with a trend toward reduced cerebrovascular mortality.[16] The vitamin E dose was also low (30 mg/day), and the population studied was very different from Western populations, having a lower risk of cardiac events and possibly an overall lower consumption of dietary antioxidants. Furthermore, the study design does not allow the identification of the particular antioxidant that contributed to the reduction in mortality.

The Cambridge Heart Antioxidant Study (CHAOS) is a secondary prevention study of 2002 patients with

Table 1 *Emerging cardiovascular risk factors and new preventive strategies*

Emerging cardiovascular risk factors	New preventive strategies
"Normal" cholesterol, blood pressure, and blood glucose	Lower thresholds of treatment in high-risk individuals
Oxidation of LDL cholesterol	Antioxidants (such as vitamin E)
Activation of the renin-angiotensin-aldosterone system	Angiotensin-converting enzyme inhibitors
Hyperhomocysteinemia	Folic acid, vitamin B_6, vitamin B_{12}
Abnormalities of coagulation:	
Fibrinogen	New antithrombotic approaches (such as preventive use of warfarin, new antiplatelet drugs)
Factor VII	
von Willebrand factor	
Plasminogen activator inhibitor-1	
Lipoprotein Lp(a)	Niacin, estrogens
Postmenopausal state	Estrogens, selective estrogen receptor modulators
Chronic infection and inflammation	Antibiotics, anti-inflammatory agents
Genetic abnormalities	"Targeted" treatment aimed at specific genes or their phenotypic expression
Nutritional factors	
Psychological factors	
Environmental factors	
Socioeconomic factors	

coronary atherosclerosis, randomly assigned to treatment with vitamin E, 800 IU daily or 400 IU daily or placebo. It reported marked reductions in nonfatal myocardial infarction (77%, 53% to 89%; P<0.001) and in the combined end point of any major cardiovascular event (47%, 17% to 66%; P=0.005).[17] Although the results are encouraging, this study has many methodological problems and remains inconclusive. The study groups were not balanced at baseline, and follow-up may not have been complete. The duration of the study was short (median of 510 days), yet the observed magnitude of benefit with vitamin E was large; the experimental and epidemiological data make such a large effect unlikely. Total mortality was slightly higher in the α-tocopherol group than in the placebo group (3.5% vs 2.7%, P=0.31). Therefore, it would be premature to conclude that vitamin E use reduces coronary risk, and routine use of vitamin E should await the results of the ongoing large trials.[9]

Other antioxidants

β-Carotene has been evaluated in three large primary prevention trials in men, all of which failed to show any reduction in the risk of cardiovascular events and cancer (Table 2).[13,18,19] Furthermore, in two studies there were concerns about an increased risk of cancer. These data suggest that raised concentrations of β-carotene may have been markers associated with other cardioprotective factors.

There have been no large trials of vitamin C supplementation. In a trial of 578 patients admitted to a geriatric hospital, supplementation with 200 mg of vitamin C daily did not reduce mortality at 6 months.[21] In the Chinese trial discussed above, there was no reduction in total mortality and in mortality from cerebrovascular disease in people randomly assigned to treatment with a combination of vitamin C and molybdenum.[16]

Probucol is a lipid-lowering agent that also reduces high-density lipoprotein cholesterol and has potent antioxidant properties. In the Probucol Quantitative Regression Swedish Trial (PQRST), probucol failed to retard progression of femoral atherosclerosis.[22] More recently, a reduction in restenosis rates after coronary angioplasty was reported in a randomized trial of probucol,[23] stimulating renewed interest in this agent; this study has several limitations, however, and conclusions should await confirmation in additional trials.

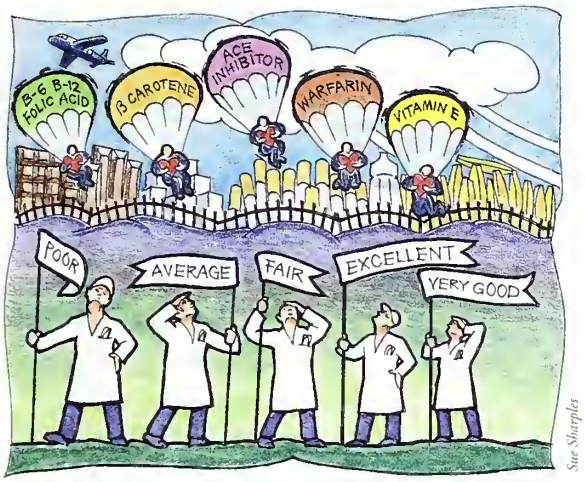
Summary

Although it is attractive, the antioxidant hypothesis has not been proven in clinical trials. The most promising data relate to vitamin E, but these are inconclusive and do not warrant its widespread use at present. The strong biological rationale and epidemiological data relating antioxi-

dants to lower cardiovascular risk justify ongoing trials of vitamin E and experimentation with new antioxidant agents, to further evaluate this hypothesis.

IMPACT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Experimental and clinical studies show that angiotensin-converting enzyme inhibitors may reduce cardiovascular risk through cardioprotective and vasculoprotective effects mediated by blocking both circulating and tissue renin-angiotensin systems, as well as by bradykinin potentiation.[24] Angiotensin-converting enzyme inhibitors are antiproliferative, have antimigratory effects on smooth muscle cells, improve endothelial function, may act as antioxidants, and act as antithrombotic agents by decreasing platelet aggregation and enhancing endogenous fibrinolysis.[24-26] Several epidemiological and genetic studies have shown a link between the renin-angiotensin system and the risk of myocardial infarction,[27,28] although these findings have not been confirmed in other reports and remain controversial.[29,30]



Risk reduction

Randomized clinical trials in symptomatic and asymptomatic patients with documented coronary heart disease and left ventricular dysfunction who were treated with angiotensin-converting enzyme inhibitors for approximately 40

Table 2 *Large randomized trials of antioxidant vitamins*

Trial	Study participants	Follow-up (years)	Vitamin dose	Outcomes	% Reduction in relative risk (95% CI)
Trials of vitamin E					
α-Tocopherol β-Carotene Cancer Prevention Study (ATBC)[13-15]	29,133 male smokers in Finland	6.1	50 mg/day	Total mortality Death from cardiovascular disease Angina	−2 (−9 to 5)† 2 (−8 to 11) 9 (1 to 17)
Chinese study[16]	29,584 adults in Linxian province	5.2	30 mg/day*	Total mortality Death from cerebrovascular disease	9 (0 to 17) 9 (−8 to 24)
Cambridge Heart Antioxidant Study (CHAOS)[17]	2002 patients with coronary artery disease in the UK	1.4	800 IU/day or 400 IU/day	Total mortality Death from cardiovascular disease Nonfatal myocardial infarction	−29 (−119 to 24) −10 (−96 to 39) 77 (53 to 89)
Trials of β-carotene					
α-Tocopherol β-Carotene Cancer Prevention Study (ATBC)[13, 14]	29,133 male smokers in Finland	6.1	20 mg/day	Total mortality Death from cardiovascular disease Death from cancer	−9 (−17 to −2)† −11 (−23 to 1) −9 (−23 to 3)
β-Carotene and Retinol Efficacy Trial (CARET)[18]	18,314 male smokers, former smokers, and workers exposed to asbestos in the US	4.0	30 mg/day‡	Total mortality Death from cardiovascular disease Death from cancer	−17 (−33 to −3) −26 (−61 to 1) −46 (−100 to −7)
Physicians Health Study (PHS)[19]	22,071 male physicians in the US	12.0	50 mg/alternate days	Total mortality Death from cardiovascular disease Death from cancer	−2 (−11 to 7) −9 (−27 to 7) −2 (−18 to 11)
Skin Cancer Prevention Study (SCPS)[20]	1188 men and 532 women in the US	8.2	50 mg/day	Total mortality Death from cardiovascular disease Death from cancer	−3 (−30 to 18) −16 (−64 to 18) 17 (−29 to 56)

* In addition to vitamin E, selenium and β-carotene supplements were used.
†Minus sign indicates an increased risk.
‡Patients randomly allocated to β-carotene also received 25,000 U/day of retinol (vitamin A).

Table 3 *Effects of angiotensin-converting enzyme (ACE) inhibitors on myocardial infarction in patients with low ejection fraction*

Trial	Patient characteristics	Number (%) with myocardial infarction		% Reduction in relative risk (95% CI)	P value
		ACE inhibitor	Placebo		
Acute Infarction Ramipril Efficacy Study (AIRE)[31]	Clinical evidence of heart failure soon after infarct	81 (8.0)	88 (8.9)	9 (−22 to 35)*	>0.05
Trandolapril Cardiac Evaluation Study (TRACE)[32]	Left ventricular ejection fraction ≤35% soon after infarct	97 (11.1)	111 (12.7)	14 (−10 to 31)	>0.05
Studies of Left Ventricular Dysfunction (SOLVD)[33]:					
Prevention	Left ventricular ejection fraction 235% without heart failure	161 (7.6)	204 (9.1)	24 (6 to 38)	0.01
Treatment	Left ventricular ejection fraction ≤35% with heart failure	127 (9.9)	158 (12.3)	23 (2 to 39)	0.02
Survival and Ventricular Enlargement Trial (SAVE)[34]	Left ventricular ejection fraction ≤40% soon after infarct	133 (11.9)	170 (15.2)	25 (5 to 40)	0.05
Total				**23 (11 to 32)**	

*Long-term follow-up of the UK component of AIRE (AIREX) showed a significant reduction in fatal myocardial infarctions.

months found a significant reduction in the risk of myocardial infarction. Pooled analyses of the five major trials of angiotensin-converting enzyme inhibitors in patients with a low left ventricular ejection fraction identified a 23% reduction in the risk of myocardial infarction associated with treatment with angiotensin-converting enzyme inhibitors (Table 3). In addition, reductions in other ischemic end points were also significant in treated patients (hospital admissions for unstable angina in the Studies of Left Ventricular Dysfunction [SOLVD] Trials, 20%, 9% to 29%; P=0.001; revascularization procedures in the Survival and Ventricular Enlargement Trial [SAVE], 24%, 6% to 39%; P=0.01). Because these trials were conducted in patients with a low left ventricular ejection fraction or symptomatic heart failure and who were likely to have raised concentrations of renin and angiotensin, these data cannot be extrapolated to other populations of patients. The reduction in ischemic events was seen in several different subgroups, however, and was not explained by the hemodynamic action of the angiotensin-converting enzyme inhibitors alone. The role of these drugs in preventing myocardial infarction in high-risk patients with preserved left ventricular function is under investigation in several large clinical trials.[35]

Summary

Angiotensin-converting enzyme inhibitors are currently indicated in all patients with clinical manifestations of heart failure and in individuals with asymptomatic left ventricular dysfunction. These agents also have a proven role in the treatment of acute myocardial infarction, hypertension, and diabetic nephropathy. Although promising, the preventive use of angiotensin-converting enzyme inhibitors in high-risk individuals with preserved left ventricular function should await the results of ongoing large clinical trials.

HOMOCYSTEINE AND VASCULAR DISEASE

Homocysteine, an amino acid containing sulfur, is produced during catabolism of the essential amino acid methionine. It can be irreversibly degraded by cystathionine β-synthase; the process requires vitamin B_6 as a cofactor. It can be remethylated to conserve methionine in a process requiring methionine synthase and methylcobalamin (vitamin B_{12}) as cofactors and methyltetrahydrofolate reductase (MTHFR) as a cosubstrate. This metabolic pathway requires an adequate supply of folate and the enzyme MTHFR. Genetic and acquired abnormalities in the function of these enzymes, or deficiencies in folate or vitamin B_6 or B_{12} cofactors, can therefore lead to raised concentrations of homocysteine. Extremely high concentrations are accompanied by homocysteinuria and are caused by rare genetic enzyme deficiencies. People with these distinct genetic abnormalities typically develop severe premature atherosclerotic and thromboembolic

disease, which led McCully to formulate the homocysteine theory of atherosclerosis.[36] More recently, a role for modest increases in homocysteine, caused by a variety of genetic, physiological, pathological, and nutritional factors, has been proposed in the etiology of atherosclerotic and thromboembolic vascular disease.

Vascular injury has been experimentally induced by homocysteine. Typical features include endothelial dysfunction due to direct, toxic endothelial cell damage and impaired production of nitric oxide; smooth muscle cell proliferation; increased production of reactive oxygen radicals; increased susceptibility of LDL cholesterol to oxidation; and increased thrombogenicity.[37]

Graded relation to risk

A large number of investigations, mostly cross-sectional or retrospective case-control epidemiological studies, found associations between raised concentrations of homocysteine and increased cardiovascular risk. A meta-analysis of the major epidemiological studies up to 1995 reported a linear, independent relation between homocysteine concentrations and cardiovascular risk.[38] Every 5-µmol/l increment in homocysteine was found to be associated with an increased risk of coronary artery disease (odds ratio = 1.7, 1.5 to 1.9), of cerebrovascular disease (1.5, 1.3 to 1.9), and of peripheral vascular disease (fewer studies available and less robust quantitation of risk). Importantly, a graded risk of adverse cardiovascular events throughout the "normal" range of homocysteine concentrations was shown, suggesting that even people with "normal" homocysteine concentrations might benefit from treatments that lowered homocysteine (a similar relation to cardiovascular risk as cholesterol).

More recently, the European Concerted Action Project reported an increased relative risk per 5-µmol/l increment in fasting total homocysteine concentration of 1.35 (1.1 to 1.6) for men and 1.42 (0.99 to 2.05) for women,[39] and Nygard et al. found a strong graded relation between homocysteine concentration and mortality in patients with angiographically confirmed coronary artery disease.[40] Low dietary intake as well as low circulating concentrations of folate and vitamins B_6 and B_{12} have also been associated with increased cardiovascular risk, presumably due to resultant hyperhomocysteinemia.[41,42] Prospective cohort studies have not always found a consistently clear relation between raised homocysteine concentrations and cardiovascular risk.[43]

Homocysteine can be easily and effectively reduced by supplementation with folic acid alone or in combination with vitamins B_6 and B_{12}. These represent simple, inexpensive, and generally risk-free interventions, but clinical trials of homocysteine lowering have not been conducted thus far. Several randomized clinical trials evaluating the impact of folate supplementation alone or in combination with vitamins B_6 and B_{12} in reducing major clinical cardiovascular events and on the progression of atherosclerosis are currently underway.

Summary

The current experimental and epidemiological data suggest that reducing concentrations of homocysteine represents an effective, cheap, and simple intervention. Until confirmation from clinical trials is available, it seems prudent to ensure adequate dietary intake of folate and vitamins B_6 and B_{12}.

Conclusions

This review summarizes the evidence on antioxidants, modulation of the renin-angiotensin axis, and reducing homocysteine concentrations as potential preventive cardiovascular interventions. These areas are promising, but definite conclusions must await the results of randomized clinical trials. Other promising preventive strategies include aggressive lowering of blood glucose in patients with diabetes and in people with only modest increases in plasma glucose; postmenopausal use of hormone replacement therapy and of selective estrogen receptor modulators; use of antibiotics; modification of determinants of coagulation; enhancing fibrinolysis; lowering lipoprotein Lp(a) concentrations; and modifying psychosocial factors.

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TOPIC IN REVIEW

Care of dying patients: beyond symptom management

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"...the secret of the care of the patient is in caring for the patient."
—Francis Weld Peabody, 1927

INTRODUCTION

Although many people have an ideal vision of death—they die at home, comfortable, surrounded by loved ones—the majority of Americans still die in the hospital, in pain, with their wishes unheeded by their physicians.[1,2] Physicians have a critical role to play in helping patients achieve the kind of death they want.

In a study by Hanson,[3] family members of patients who had died identified ways to improve end-of-life care. Notably, they wanted to talk to physicians about death and dying, including treatment options and alternatives, prognosis, advance directives, and death. Patients and families wanted psychosocial support, particularly access to the physician, through this difficult and important time. Although symptom management is a crucial first step identified by dying patients and their families, this article focuses on care beyond symptom control. It begins with a review of communication with dying patients and psychosocial support. Next, it covers hospice, an underused service that can provide many of the services that patients and families want at the end of life. The last section examines what physicians can do for families and themselves after a patient dies to help deal with the grief and loss.

COMMUNICATING ABOUT ILLNESS AND DEATH

One fundamental part of caring for dying patients is communicating about illness and death (see box). The best data regarding communication about illness and death are those regarding advance directives, perhaps because advance directives are concrete, well defined, and easy to study. We can extrapolate important lessons for the care of dying patients from studies of advance directives.

Communicating about illness and death

- Listen
- Make empathic statements
- Avoid jargon
- Elicit the patient's values and goals of care
- Offer information about prognosis
- Discuss death explicitly
- Maintain cultural sensitivity

Many physicians are reluctant to talk to patients about death for fear of upsetting them or taking away hope.

Summary points

- Physicians can improve their care of dying patients.
- Physicians can improve their communication about illness and death by listening more than speaking, avoiding jargon, encouraging patients to share their values and goals of care, and making empathic connections with patients.
- Physicians must offer psychosocial support, including making specific statements to a patient indicating that the physician will not abandon him or her, discussing hope, helping patients to attend to important relationships, and encouraging spirituality.
- Hospice is an invaluable and underused resource for providing high-quality, compassionate care to dying patients and their families.
- Physicians must attend to the impact of a patient's death on the family and on themselves.

Despite these concerns, McCormick and Conley found that dying patients wanted to talk about illness and death.[4] Other studies demonstrate that a majority of patients want to talk about advance directives.[5,6] Despite this desire, few patients had spoken with their physicians about advance directives because they were waiting for the physician to raise the issue.

Even when these discussions do occur, they are far from ideal. Tulsky et al., in a review of tape recordings of medicine residents discussing code status with hospitalized patients, found that in the average 10-minute conversation, the physicians used jargon, talked nearly 75% of the time, missed opportunities for empathic connection, and did not elicit the patient's values and goals of care or offer information about prognosis.[7]

Based on these findings, physicians can take steps to improve communication with dying patients. First, physicians can listen more. Although there is important information for physicians to share, physicians must encourage the patient to talk and then listen to their concerns. Physicians should refrain from using jargon. In addition, rather than focusing on specific decisions such as instituting vasopressors or dialysis, physicians may find it more helpful to elicit the patient's general values and goals to give a context for care and interventions. One way to elicit this information is to ask, "When you think about getting very sick, what worries you the most?"

Similarly, asking the patient to identify a surrogate decision maker is critical for preparing for the time when the patient may not be able to make decisions on his own behalf. Beginning such conversations by eliciting the patient's choice of a surrogate offers a less threatening

Nan Goldin

Joseph at Cabrini Hospice, NYC 1995

way to initiate the discussion. One way to elicit the patient's choice of a surrogate is to ask, "If you were so sick that you could not talk to me directly, who should I talk with to help me make decisions about your care?"

Physicians should be alert to opportunities for empathetic connection. Empathic statements not only encourage patients to share more of their concerns but also express physicians' care for their patients.

Patients also need explicit information about prognosis for decision making. Studies have shown that elderly patients are overly optimistic about chances for survival after CPR and, when their misperceptions were corrected, they were less likely to want CPR.[8,9] McCormick and Conley found that dying patients said they had to infer prognosis from comments and nonverbal communication from doctors and nurses and would have preferred straight talk.[4] Information about prognosis allows patients to make plans and attend to tasks such as seeing family, having visitors, or writing wills.

McCormick and Conley also learned that patients wanted to discuss death explicitly. Such discussions help define the patient's unique view of a good death. They elicit the patient's fears and concerns about death and allow the physician to address them directly. One way to elicit this information is to say, "Many patients with this condition tell me they think about the possibility of dying. They have questions about this. How about you?"

Finally, these discussions must respect the patient's cultural background and be sensitive to differing notions about the implications of discussing death and dying. For instance, in Navajo culture it is believed that giving a patient an explicit prognosis will cause the prediction to come true.[10] One way to raise the issue of prognosis while allowing the patient to refuse the information is to allow the patient to give "informed refusal." A physician might say, "I have information about your condition. Some patients want to know the details and some prefer not to know or to have me talk to a family member. How do you feel?" Such a statement respects the patient's cultural beliefs and allows the patient to waive his right to information while not assuming that he will.

PSYCHOSOCIAL SUPPORT

"Not every patient can be saved, but his illness may be eased by the way the doctor responds to him....He has little to lose and everything to gain by letting the sick man into his heart. If he does, they can share, as few others can, the wonder, terror and exaltation of being on the edge of being."

—Anatole Broyard[11]

Traditionally, support was all that physicians could offer patients. With advances in medical technology, many physicians downplay the fact that such support can be critical to the care of dying patients.

In communicating about illness and death, we offer patients information, yet information without support can be distressing. In a study of HIV-positive patients, Chesney et al. showed that patients offered only information about HIV were more distressed than patients offered information and psychosocial support.[12]

Nan Goldin

Joseph's medicine

Quill and Cassel write about nonabandonment and the importance of being with the patient throughout the course of illness.[13] Specific statements such as, "I will be your doctor throughout this illness," and "I will take care of you, whatever happens," can do a great deal to relieve anxiety and reassure patients that they will not be abandoned by their doctor when they need him or her the most.

Ultimately, patients abandon physicians when they die. In response, physicians may withdraw from patients before they die. Physicians start looking ahead too early and pull away so they are not hurt when their patients die, because they incorrectly conclude there is nothing more they can do, or because they have difficulty dealing with death and facing their own mortality. It is critical, however, for the physician to be with the patient through the dying process. There are several ways for physicians to make sure they don't abandon their patients.

First, physicians can provide dying patients with access. A physician who gives a patient a beeper number or direct phone number and who makes home visits and phone calls makes a powerful and meaningful statement about commitment to the patient. In addition, scheduling office visits can be very important to dying patients. Although such a visit may be too burdensome for some patients, many dying patients want to come to see the doctor. There is power in presence. For patients who are too ill to visit the doctor, a home visit can be critical in managing the illness and making the patient feel cared for.

Hope is another important component of support. Many people fear that talking about dying will rob patients of hope. As physicians, we do not create hope or take hope away. We can, however, encourage and uncover hope for patients. A simple way to help patients identify hope is to ask, "When you think about the future, what do you hope for?" Patients often give humbling and profound responses like, "I hope to die at home," or "I hope to live to see the birth of my grandchild." Such statements offer insights into a patient's values and goals and create opportunities to encourage hope.

Increasingly, death is seen as a stage of growth and development in which people have tasks to complete. Ira Byock writes that there are five statements each person needs to make before dying: "Forgive me," "I forgive you," "Thank you," "I love you," and "Goodbye."[14] The process of making these statements brings closure and attends to important personal relationships.

Another part of growth and development at the end of life involves patients telling their life stories. For many people the existential angst at the end of life is not about dying but about never having lived. People fear being forgotten. Telling their stories is a way of being remembered by loved ones and of bringing further closure. Physicians can encourage patients to use a tape recorder, journal, dictation, or videotape to tell the stories of their lives to be shared by loved ones in the future.

Finally, the role of spirituality has been gaining more and more attention in the care of dying patients and in medicine generally. There is evidence that dying patients who are spiritual or religious have less anxiety.[15] Although this fact does not suggest that physicians should tell patients to become religious, it does support physicians' encouragement of spirituality in patients already inclined that way. In addition, spirituality can offer dying patients comfort and meaning. Although physicians may have no specific religious or spiritual training, many of the issues patients raise with physicians have a spiritual dimension. Questions such as "Why is this happening to me?" have a decidedly spiritual quality. When a physician discusses spirituality, it may help legitimize the issue for the patient. There are several ways to raise the issue of spirituality (see box).

Nan Goldin

Joseph laughing, NYC 1995

Discussing spirituality

"From where do you draw your strength?"
"What role does religion or spirituality play in your life?"
"Do you believe in a God or higher power?"
"Do you pray?"
"Do you attend a synagogue or church?"

HOSPICE

It is important to realize that physicians cannot provide all of the services and support that are needed to care for dying patients. The best end-of-life care occurs when there is a team of providers caring for the patient. Nurses, social workers, pharmacists, chaplains, physical therapists, and psychologists, among other members of the healthcare team, play a critical role in providing comprehensive, compassionate care at the end of life. One way to marshal this type of multidisciplinary support is through hospice.

Hospice focuses on palliation of symptoms and communication about illness and death. It provides psychosocial support to patients and their families. The only randomized control trial of hospice showed that, compared with usual care, hospice increased patient satisfaction and decreased family anxiety.[16]

Despite the usefulness of hospice, it is underutilized. The average length of stay in hospice is only 36 days, although under the Medicare hospice benefit, physicians need to certify only a six-month prognosis for patients to qualify.[17] Even more troubling is that 15% of patients die within 7 days of admission to hospice. Such patients could have reaped more benefit from hospice. Unfortunately, too few patients afford themselves of hospice, and most of those who do, come to it late. Physicians may be reluctant to talk about hospice for fear of taking away hope. Nonetheless, there are ways to raise the issue of hospice that are less threatening to patients (see box).

Discussing hospice

"Something I discuss with all my patients with cancer is hospice. Have you heard of hospice?"

"Hospice may not be right for you now, but I wanted you to hear about it so you know all the options. It may be right for you later."

"It sounds like what concerns you the most is trying to get your wife [or husband] more help at home as you get sicker. One way to provide more support for both of you is through hospice."

AFTER DEATH

The work of the physician does not end when the patient dies. In many instances, the family also becomes our patient and must be attended to after the patient has died.

Caring for families

It is important to attend to the family and provide comfort and support. One important step is to call the family several weeks after the patient has died. Besides showing respect and caring, such calls allow families to ask questions about the death. Without such an opportunity, many families may wonder and carry guilt for years about whether there was something that could have been done differently. Many physicians choose to send condolence cards to express caring for the family, acknowledge their loss, and relate how much the patient meant to him or her. In addition, attending the funeral or memorial service can give the physician closure and can mean a great deal to the family. Finally, some physicians may contact the family on the anniversary of the patient's death. Hospices do so routinely, in addition to providing psychosocial support for a year after the patient's death.

Support for physicians

Physicians and staff caring for dying patients also need support. Physicians often have the luxury of being able to write an order to withdraw life-sustaining interventions and walk away, leaving the nurse and respiratory therapist alone with a dying patient. At such moments, the physician's presence can be crucial to patients for managing unexpected distress or discomfort. The physician's presence can also be supportive to staff and emphasizes the team approach to patient care.

Rituals can help acknowledge and deal with death. Some physicians use prayer, meditation, time alone, journal entries, or a quiet walk to acknowledge and contemplate a patient's death. In addition, discussing patients and circumstances of their death with colleagues helps to deal with sadness. Although it may be difficult to talk about a patient's death, not talking about it can take a cumulative toll on a career in medicine.

CONCLUSION

Physicians can help their patients and themselves find comfort and meaning at the end of life and help transform a difficult period into a time of meaning and connection.

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MEDICINE CABINET

Just say yes: the use of opioids for managing pain at the end of life

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INTRODUCTION

Many dying patients have severe pain at the end of life.[1] In the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT), 50% of conscious patients had moderate to severe pain at least half the time in their last three days of life.[2] Studies of outpatients reveal that from 12% to 71% of dying patients have significant pain in the last week of life.[3-5] Despite these statistics, pain is a symptom for which excellent, well-proven treatments are readily available.

ASSESSMENT OF PAIN

Unfortunately, physicians do a poor job of assessing, relieving, and predicting their patients' pain.[6] Certain physician attitudes are associated with better pain control, such as insisting on total pain relief, remaining liberal with pain medications, and believing that their patients have pain. There is no pain meter and no objective test for pain. The only reliable way to quantify pain is to ask the patient, using pain scales such as those in Figure 1, and then to believe the patient.

Pain scales can be translated into any language. Pictures can be helpful for patients for whom you do not have a written scale in their language. These scales are reliable, and they make patients' ratings reproducible. It is crucial to assess pain before and after an intervention. It is also important to note how long the relief lasted. These parameters allow the physician to adjust medications accordingly. The physician should adjust the dose of medicine to control the intensity of pain and should adjust the interval between doses so that pain relief is uninterrupted. Physicians should never treat pain on an as-needed basis when it is severe or moderately severe, chronic, or anticipated. It is best to write for around-the-clock dosing to maintain continuous analgesia. It is easier and takes less medicine to keep the pain away than to subdue it once it returns. Another important goal of pain assessment is to determine the nature and cause of pain because treatment will vary by etiology. In particular, neuropathic pain—often described as burning, electrical, pins-and-needles, or tingling, and sometimes associated with subjective numbness—might respond better to tricyclic antidepressants or anticonvulsants.

TREATMENT OF PAIN

The World Health Organization (WHO) analgesic ladder can be helpful in choosing a medication (see box).[7] The higher the step on the ladder, the stronger the analgesic and the greater the chance for adverse effects. Although many patients near the end of life will have moderate to severe pain, some will have only mild pain. For these patients, Step 1 agents such as acetaminophen, aspirin, or nonsteroidal anti-inflammatory drugs (NSAIDs) can be very useful. Acetaminophen (650 mg orally every 4 hours) is effective in mild to moderate pain. Because of the risk of hepatic toxicity, doses should not exceed 4 grams per day chronically or 2 grams per day in patients with hepatic dysfunction. Whereas acetaminophen is antipyretic and analgesic only, aspirin and NSAIDs are anti-inflammatory as well. In addition to their use for mild to moderate pain, these drugs are useful in conjunction with opioids, particularly for patients with bony pain from metastases. Their untoward effects include gastrointestinal irritation and increased risk of bleeding. Nonsteroidal anti-inflammatory drugs can also cause kidney damage and hepatic dysfunction.

World Health Organization analgesic ladder

Step 1: acetaminophen, aspirin, NSAIDs

Step 2: codeine, hydrocodone

Step 3: morphine, hydromorphone, methadone, oxycodone, fentanyl

Consider adjuvants at each step.

Moderate to severe pain

For patients with moderate to severe pain (a score of five or more on a visual analog scale)[7] or for whom the above treatments no longer work, opioids are the appropriate treatment. As shown in the WHO analgesic ladder, Step 2 opioids include codeine and hydrocodone. One limitation to their use is the ceiling effect caused by the acetaminophen or aspirin found in the most common preparations of these drugs. Step 3 opioid analgesics include morphine, hydromorphone, methadone, oxycodone, and fentanyl. One important advantage of these drugs is that they have no ceiling effect. Morphine is a good first choice when using opioids because it offers several advantages: (1) it can be given orally, rectally, subcutaneously, or intravenously; (2) it is easily titrated; and (3) it is effective for dyspnea. A reasonable starting dose would be 2 to 6 mg intravenously or 4 to 18 mg orally every 3 to 4 hours. Patients who use opioids chronically will need to receive their baseline dose plus an additional 25% to 50% to treat acute pain. When first titrating a dose of an opioid, it is best to use shorter-acting preparations. Once you reach a stable dose, it is best to switch to a long-acting preparation. Occasionally patients will need to switch from one type of opioid to another, due to side effects such as nausea, urinary retention, agitation, or rash, or

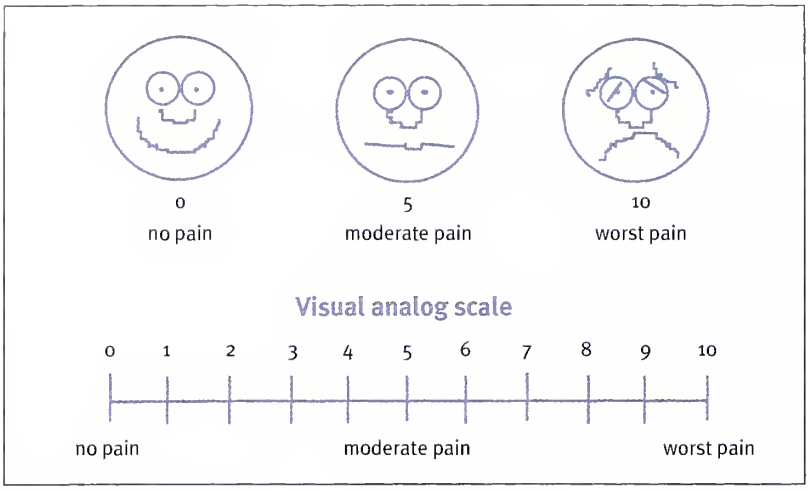

Figure 1 *Pain assessment tools*

from one route of administration to another. Equianalgesic dosing charts, like the ones in Table 1,[8] can help with the conversions. When switching between opioids, it is best to dose the new medication initially at one third to one half the equianalgesic dose.[9]

When feasible, the oral route of administration is preferred because it is easier for patients and families, does not require trained staff, does not transmit infection the way needles can, and is less costly. Morphine elixir can be effective when placed in the mouth, even for patients who are too weak to swallow. To do so, it is helpful to use a syringe and gently place the medicine against the buccal mucosa. Although morphine is hydrophilic and cannot be absorbed directly in the mouth, it does reach the stomach. This route should not be used in patents with complete esophageal obstruction, however.

Continuous infusions

Although not every dying patient needs a continuous opioid infusion, such treatment can be useful for controlling pain for (1) patients with persistent nausea and vomiting or severe dysphagia; (2) patients with delirium, confusion, stupor, or other disorders that impair the patient's ability to swallow and increase the risk of aspiration; (3) patients with severe pain who need rapid titration to control the pain; and (4) patients on high doses of oral medications that require swallowing many tablets. Although a major advantage of intravenous infusions is that they provide the most consistent level of analgesia, they also require intravenous access and an experienced, trained individual to administer them. Usually it is possible to achieve the same degree of pain control through the use of long-acting oral opioid preparations or, once the patient is on a stable regimen, transdermal fentanyl. Avoid the intramuscular route, as it is a painful and unreliable way to administer opioids.

Table 1 *Equianalgesic dosing*[8]

Drug	Dose (mg) equianalgesic to 10 mg SC/IV morphine		SC/IV:PO ratio	Half life (h)	Duration of action (h)
	SC/IV	PO			
Morphine	10	20-30*	2/3:1*	2-3.5	3-6
Codeine	130	200	1.5:1	2-3	2-4
Oxycodone	15	30	2:1	3-4	2-4
Hydromorphone	1.5	7.5	5:1	2-3	2-4
Methadone	10	20	2:1	15-120	4-8
Fentanyl	0.1	–†	–	1-2	1-3

* Most references use a 6:1 ratio of SC/IV to PO morphine, but that number is based on single-dose studies. For patients in steady state, it is more appropriate to use a ratio of 2/3:1.
† Oral transmucosal fentanyl is now available for acute breakthrough pain but is not used for routine pain control; therefore, no oral equivalents are given.

Patient-controlled analgesia

Patient-controlled analgesia can be accomplished by mouth or intravenous infusion. It offers the patient control over the analgesia and often results in faster and better pain control. In postoperative treatment, most of the drug is received as boluses, but in end-of-life care the majority of the opioid is given at a basal rate. Patients then use boluses to augment the basal rate, for breakthough pain or painful interventions, as when a patient with bony metastases is turned. Because the patient must be awake to control analgesia, this technique may not be suitable for terminally ill patients.

Goals of treatment

The goals of treatment are to relieve pain and maximize the patient's ability to function. To accomplish these goals, physicians and patients must work together to achieve a balance between pain control and sedation. Finding the correct balance requires discussions with patients to titrate pain relief appropriately. Many patients want to remain conscious in order to talk to loved ones and will tolerate some pain. The key is to ask the patient, believe the patient, and work with the patient. Because of the lack of a ceiling effect with Step 3 opioids, the dose of opioid medication is less important than the response of the patient in terms of pain. Lower pain scores (preferably below five) and increased function are the ultimate measures of the success of treatment.

In patients who are not communicative, moaning and grimacing can indicate the presence of pain. Such assessments are key because while in acute pain patients may manifest tachycardia, diaphoresis, and elevated blood pressure; in chronic pain vital signs may be normal.

TREATMENT OF SIDE EFFECTS

It is possible to anticipate and treat side effects of opioids to minimize any deleterious effects.

Respiratory depression

Although of great concern to patients, families, and physicians, respiratory depression is an uncommon side effect. While some respiratory depression does occur, and is used

to its advantage in patients with dyspnea, apnea is rare. Patients with underlying lung disease may be at higher risk for respiratory depression and should be closely monitored. Reducing the dose of the opioids will often be sufficient to reverse this effect. Gradual slowing of the respiratory rate is expected in patients who are imminently dying. It is important not to withhold opioids from these patients. When the primary intent is to relieve pain, the use of opioids, even to the point of suppressing respiration, is ethically appropriate. Physicians have an ethical obligation to relieve pain.

Sedation

Tolerance to the sedative effects of opioids develops quickly. If sedation persists and the patient wishes to be more alert, dose reduction, if possible, is the best approach. Occasionally, switching to a different opioid will lessen sedation. Dextroamphetamine, 2.5 to 10 mg orally twice daily, or caffeinated beverages can counteract sedation.

Constipation

Constipation can be distressing to patients and can usually be prevented by starting a bowel regimen at the same time that you begin an opioid. In addition to the steps outlined here (see box), the combination of senna (a laxative that stimulates the bowel, two tablets by mouth once or twice a day) and ducosate sodium (a stool softener, 250 mg by mouth twice a day) is a good starting regimen for patients on opioids. Quickly titrate these medications upward in the absence of a bowel movement. More severe constipation may require bisacodyl (10 to 30 mg orally or one or two suppositories daily) or even lactulose (30 ml orally twice a day). In all circumstances, early prophylactic treatment is far better and easier than trying to relieve constipation later.

Prophylaxis of constipation[14]

- Maintain good general symptom control
- Encourage activity
- Maintain adequate oral fluid intake
- Maximize the fiber content of the diet
- Prescribe a bowel regimen using senna and a stool softener

Nausea and vomiting

Nausea and vomiting occur in up to a third of patients who receive opioids and usually resolve after 72 hours. Changing opioids will often control the symptoms. In addition, antiemetics such as prochlorperazine (10 mg orally every 8 hours or 25 mg rectally every 8 hours) or metoclopramide (10 mg orally up to four times daily) can be effective.

Urinary retention

Urinary retention can also occur, although it is most common with the spinal administration of opioids. Stopping adjuvant drugs such as tricyclic antidepressants, which can exacerbate the problem, may provide relief. If the problem persists, switch to a different opioid.

Pruritis

Pruritis is seen more commonly with intravenous than oral opioids. Diphenhydramine, 25 mg orally up to four times a day, can be effective in relieving pruritis.

ADDICTION

Reassure patients and families that addiction—the psychological dependence on opioids—is not a problem for dying patients and that compassionate care may require the liberal use of opioids. In studies of more than 22,000 patients receiving opioids for chronic pain, fewer than one in 1000 developed addiction.[10-13] Physical dependence, however, in which patients who chronically take opioids suffer a withdrawal syndrome on abrupt discontinuation of the medications, is expected and is not a sign of addiction.

CONCLUSION

Physicians can do a great deal to relieve pain for patients at the end of life by believing the patient, being willing to prescribe opioids, and committing to pain relief. Patients are then able to focus on the important tasks at the end of life.

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TOOLBOX

Beyond breaking bad news: how to help patients who suffer

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"He who has a why to live can bear with almost any how."
—Friedrich Nietzsche

Expert advice

Despite the fact that clinicians are responsible for delivering bad news, this skill is rarely taught in medical schools or residencies in the United States, and clinicians are generally poor at it.[1-4] Experienced clinicians who have offered recommendations for delivering bad news well agree on many points.[5-8] The box below lists the clinician's most important goals for the initial breaking of bad news, as cited in the medical literature. The box on the facing page summarizes specific recommendations offered in the literature for delivering bad news, organized into a simple mnemonic ("ABCDE"). Experts also point out that clinicians invariably respond with their own feelings about the bad news.[9]

Initial goals in delivering bad news

- Allow emotional ventilation
- Achieve a common perception of the problem
- Address basic information needs
- Address immediate medical risks, including suicide
- Respond to immediate discomforts
- Ensure a basic plan for follow-up
- Anticipate what has not been talked about
- Minimize aloneness and isolation (reassure about nonabandonment)

Breaking bad news is sometimes seen as a skill that clinicians can master with attention to the words, setting, and attitude with which they deliver upsetting information. Beyond breaking the bad news, however, clinicians also are called on to help manage its consequences—a task that requires not just expert advice and training, but also attention to patients' existential and spiritual issues.

Suffering and meaning

Physician Eric Cassel defined suffering as "the state of severe distress associated with events that threaten the intactness of a person."[10] In this model, the whole person is a complex integration of many parts, including the physical body, secret inner life, relationships, and sense of underlying meaning in the universe. In challenging one or more of these parts, bad news can cause suffering. For patients, bad news often threatens their identity and challenges their sense of transpersonal meaning. Thus bad news can raise profound spiritual issues.

Clinicians focus often on relieving patients' bodily pain, less often on their emotional distress, and seldom on their suffering. Indeed, clinicians may view suffering as beyond their professional responsibilities. But by concentrating on physical or emotional pain, clinicians may be ignoring important elements of meaning to the patient as a person, thereby intensifying suffering.

If clinicians feel unable to, or simply do not want to, address the powerful issue of patient suffering, it is appropriate to refer the patient to another professional on the healthcare team who is more comfortable in this arena. Physicians, nurses, psychologists, social workers, and chaplains all have a role in helping patients who suffer and can support each other in providing care to the patient.

Throughout the process of dealing with suffering, the core task of the clinician must be to understand the patient's response to the bad news and the meaning ascribed to it. This understanding can come only from a detailed and tolerant exploration of the patient's unique experience of suffering.[5,10] The clinician's commitment to nonabandonment and to listening openly to the patient is necessary to being able to accompany the patient through the profound challenges of bad news, especially at the end of life.[11] Indeed, it is the trust possible in the patient-clinician relationship that allows clinicians to discover what may be of service to the patient.[12,13]

Summary points

- Clinicians are rarely taught how to deliver bad news.
- Following published recommendations might help clinicians to deliver bad news well.
- In addition to delivering bad news, clinicians can help patients manage its consequences.
- Important tasks include listening with compassion and understanding the meaning patients ascribe to bad news.
- Clinicians may also offer a number of specific responses to patients to help ameliorate suffering.

How can clinicians provide support and how can they help ameliorate suffering? First, clinicians can help simply by listening with compassion. Second, clinicians can provide emotional reflection and validation. Importantly, clinicians also may offer a number of specific responses to patients to help ameliorate suffering. These responses, derived from the work of Cassel and others, are divided into "inquiries" and "prescriptions" that can be offered to help catalyze

Jack Radcliffe

Sheila and Georgia

patients' thinking and gather resources for facing suffering (see box, page 262).

Finding strength

Patients may be able to bear bad news through personal strength (for example, from previous life experience) or with the strength of others (for example, in bereavement groups). Strength can help hold together the parts of a person threatened with dissolution by bad news.[10]

Clinicians may begin an inquiry into the patient's resources by asking, "When bad things have happened to you before, how did you cope?" Simply asking "What are your sources of strength or support?" will help the clinician identify the patient's need for additional resources. Asking patients "To whom will you turn for support?" may encourage patients to mobilize their own resources.

Based on an understanding of the patient's inner strengths and social supports, clinicians might "prescribe" educational reading material, support groups, and referrals to other professionals, to lend strength to the suffering patient.

Enhancing growth

The challenge of bad news or illness may be met with personal growth by the patient. The integrity of the whole person may be maintained if the person can compensate for what is lost.[10] Many involved in hospice work report the end of life to be an opportunity for personal growth by patients.[14]

Clinicians might ask, "Even though there are some things you can no longer do, what activities can you still enjoy?" With some patients, the clinician may have to search for an opening: "What about you as a person does this disease *not* affect?"

Reviewing earlier experiences of growth in a patient's life may assist the patient in identifying the processes by which he or she best learns and develops. Research into what has been possible for others at the end of life may challenge the patient's sense of limitation. Volunteer work can help some patients regain a sense of purpose and value.

Embracing the moment

Bad news often represents a threat to the future, but the resultant suffering may be preempted by embracing the present moment. For example, a patient may say, "Although I know I will get very sick from my illness in the days ahead, today I feel well enough to enjoy time with my grandchildren." A patient focused on current feelings, experiences, and meaning may avoid the pain caused by considering a future darkly circumscribed by a bad prognosis. This focus may help dissolve barriers and bring about a sense of intimacy and wholeness.[15]

Clinicians might inquire about patients' desires and current feelings, asking such things as "What do you feel like doing right now?" Alternatively, asking patients about their hopes and dreams may reveal a desire that the patient might fulfill earlier rather than later: "Is there something you've always wished you could do?" and "What's stopping you from doing it now?"

Searching for meaning in suffering

The psychiatrist Viktor Frankl wrote that "Man is not destroyed by suffering; he is destroyed by suffering without meaning."[16]

Techniques for delivering bad news well: ABCDE

Advance preparation
- Ask what the patient already knows and understands. What is his or her coping style?
- Arrange for the presence of a support person and appropriate family
- Arrange a time and place that will be undisturbed (hand off beeper)
- Prepare emotionally
- Decide which words and phrases to use (write down a script)
- Practice delivering the news

Build a therapeutic environment/relationship
- Arrange a private, quiet place without interruptions
- Provide adequate seating for all
- Sit close enough to touch if appropriate
- Reassure about pain, suffering, abandonment

Communicate well
- Be direct ("I am sorry, I have bad news")
- Do not use euphemisms, jargon, acronyms
- Say "cancer" or "death"
- Allow for silence
- Use touch appropriately
- Ask patient to repeat his or her understanding of the news
- Arrange additional meetings
- Use repetition and written explanations or reminders

Deal with patient and family reactions
- Assess patient reaction
  - physiologic responses: flight/fight, conservation/withdrawal
  - cognitive coping strategies: denial, blame, intellectualization, disbelief, acceptance
  - affective responses: anger/rage, fear/terror, anxiety, helplessness, hopelessness, shame, relief, guilt, sadness, anticipatory grief
- Listen actively, explore feelings, express empathy

Encourage and validate emotions (reflect back emotions)
- Correct distortions
- Offer to tell others on behalf of the patient
- Evaluate the effects of the news
- Explore what the news means to the patient
- Address further needs, determine the patient's immediate and near-term plans, assess suicidality
- Make appropriate referrals for more support
- Provide written materials
- Arrange follow-up
- Process your own feelings

Strategies for clinicians to help patients who suffer

1. Finding strength

- Inquire about the patient's resources:
  - "When bad things have happened to you before, how have you coped?"
  - "To whom will you turn for support?"
- Prescribe resources available to the patient:
  - Regular physician follow-up
  - Psychologist, social worker, chaplain, home-care referral
  - Reading material, videos
  - Specific organizations (e.g., the National Colitis Association)
  - Internet news groups, bulletin boards, chat rooms
  - Support groups

2. Enhancing growth

- Inquire about compensatory pleasures and skills:
  - "Even though there are some things you can no longer do, what activities can you still enjoy?"
  - "Are there things about you this disease does not affect?"
- Prescribe steps toward growth:
  - Identify times when the patient has grown in the past
  - Research what has been possible for others
  - Encourage volunteering

3. Embracing the moment

- Inquire about current feelings and desires:
  - "What do you feel like doing right now?"
  - "Is there something you've always wished you could do? What is stopping you from doing it?"
- Prescribe a redirection toward current reality:
  - Coordinate disease treatment with personal goals
  - Help set priorities
  - Teach or encourage meditation

4. Searching for meaning in suffering

- Inquire about the patient's disease model and meaning of illness:
  - "What does this news mean to you?"
  - "Does this news scare you in any way?"
  - "What do you think caused your illness?"
- Prescribe life examination exercises:
  - Journal writing, autobiography, life review
  - Revisiting the past through photos, people, travel

5. Seeking acceptance and reconciliation

- Inquire about personal dissatisfaction and estranged relationships:
  - "Where are you hardest on yourself?"
  - "Do you have any regrets in life?"
  - "Is there anyone you really want to talk to before you die?"
  - "Is there someone you've never been able to forgive?"
- Prescribe steps toward self-acceptance and reconciliation:
  - Advance care planning
  - Distribution of personal possessions
  - Communication by letter, telephone, e-mail
  - Meetings, goodbyes

6. Achieving transformation

- Inquire about spiritual and religious beliefs:
  - "Are you a spiritual or religious person?"
  - "Has illness ever changed you in a fundamental way in the past? If so, how?"
  - "Do you know anyone who was transformed in a positive way by illness?"
  - "Where do you think things are headed?"
- Prescribe movement toward transcendence:
  - Spiritual mentor
  - Prayer
  - Letters to loved ones

Searching to understand the meaning underlying bad news or at the end of life can provide solace. "In some way," Frankl wrote, "suffering ceases to be suffering at the moment it finds a meaning."[16]

Clinicians must understand the model of disease employed by the patient, as well as the patient's understanding of the meaning of the illness. Asking a patient, "Where do you think your illness came from?" might uncover the patient's beliefs regarding the cause of disease and his or her sense of responsibility for it. Patients often find comfort in learning from their clinicians that the bad news is not their fault. Asking patients, "How are you doing within yourself?" or "What does this news mean to you?" may lead to discussions that help patients begin to grapple with the meaning of their illness, giving them a sense of control.

The sufferer's question, "Why me?," is a potent one to which clinicians must respond—though not necessarily answer. Clinicians can facilitate the patient's own search for meaning by encouraging the patient to undertake an examination of his or her life and memories. The clinician might offer a prescription to keep a journal, practice meditation, or look through photograph albums.[17,18]

Seeking acceptance and reconciliation

Philosopher and priest Henri Nouwen wrote about "befriending" one's suffering as the first step toward healing.[19] In accepting suffering, a patient can claim it, become familiar with it, and, potentially, overcome it by embracing it. Consideration of the end of life sometimes prompts patients to forgive or seek forgiveness from loved ones. This forgiveness can provide the patient with an unexpected positive outcome from the experience of illness and has even led some patients to describe their cancer as a gift.[20]

Regret, guilt, and shame act as barriers to self-acceptance. A clinician may gently explore a patient's regrets or personal dissatisfaction with questions such as "Where are you hardest on yourself?" Asking directly about painful or estranged current or past relationships is appropriate for some patients ("Is there someone you really want to talk to before you die?"). Clinicians can offer to assist patients contemplating a reconciliation with an estranged loved one.

An acceptance of bad news allows patients to focus on the tasks of adjusting to their illness or on the tasks of dying, rather than fighting fruitlessly against inevitable mortality. Advance care planning encourages patients to make personal and legal arrangements for the time when they become sicker or die. Some patients at the end of life gain a sense of joy and completeness in distributing their possessions to loved ones.

Achieving transformation

Sometimes, illness and loss may be transformative. Patients can respond to bad news by growing not merely stronger but fundamentally different. In a powerful paradox, such transformation allows patients to discover a passion for life in the face of impending death.[14]

Clinicians can ask, "Are you a spiritual person?" More direct questions include "Has illness ever changed you in a fundamental way in the past? If so, how?" and "Do you know anyone who was transformed in a positive way by his or her illness?"

Although transformation through suffering is an intensely personal event, the clinician has an appropriate role in searching creatively with the patient for how good can come from bad. Clinicians may encourage religious patients to pray or may help them to seek out a spiritual mentor. Sitting with, talking with, or writing letters to loved ones often helps focus patients at the end of life on transcendent issues such as the soul, the meaning of life, and the nature of love.

Reviving the messenger

In ancient times, the bearer of the news that a battle had been lost was often killed. In a similar fashion, when reacting to bad news, some patients blame their clinicians. This desire to "kill the messenger" seems understandable if clinicians appear merely to deliver prognoses without compassion and to be locked in battle with death as an adversary rather than acknowledging death as an essential part of life.[21]

Clinicians can deliver bad news well *and* manage its consequences. Clinicians are not responsible for knowing the answers to patients' deeply personal and existential questions; they are called on to be present as witnesses to their patients' suffering and to respect the vulnerability created by the news they bear. Whether simply being present for a patient in shock after the delivery of bad news or accompanying a patient undergoing a spiritual transformation, clinicians can help meet the patient's existential needs. In working to relieve suffering, in helping patients to discover not just *how* to live but *why*, clinicians fulfill an obligation and enjoy a privilege deeply rooted in the healing tradition and sanctified by society at large.

To manage bad news well, the clinician must place his or her relationship with the patient, the strength and reality of their human bond, over the insecurity of disease, the threat of dissolution, and the fear of death. Breaking bad news is not as much a delivery as it is a dialogue between two people, both striving to discover in each other a simple faith in the future and an understanding of meaning beyond themselves.[5]

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Boo Boo with nurse

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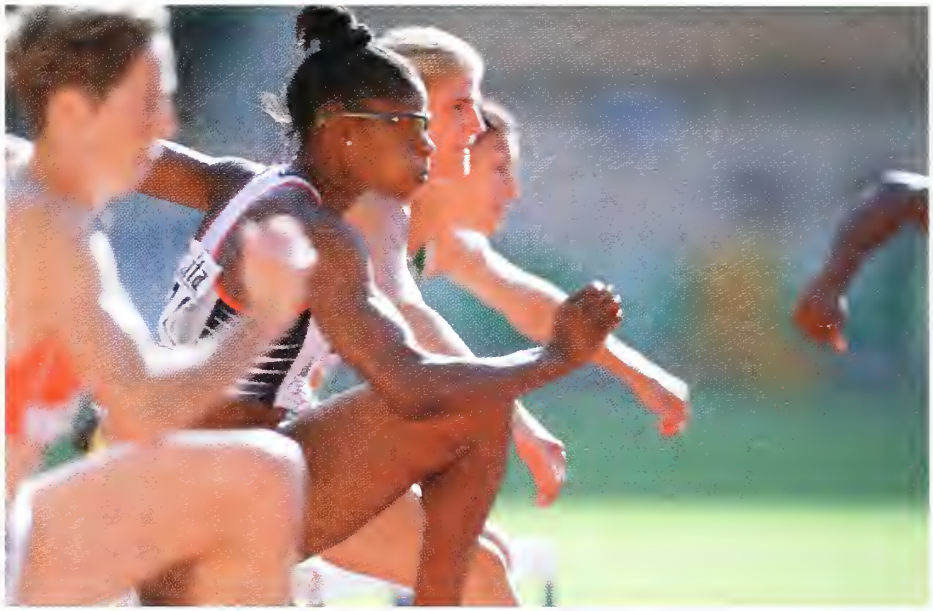
capsule

Why TB vaccines don't always work The Bacille Calmette Guérin, or BCG, vaccine protects some populations against tuberculosis but not others. This may be because the original live attenuated vaccine has evolved over the years into an array of different substrains that may have different immunogenicity (Science 1999;284:1520-1522). A genome analysis of known daughter strains shows that at least five fragments of DNA have been lost along the way, and scientists must now try to link the changes to BCG's variable performance.

What is the effect of exercise on primary dysmenorrhea?



Michael Steele/EMPICS

Denise Lewis during the hurdles discipline at the Athletics World Championship in Seville.

In the past 15 to 20 years, research into the link between physical activity and menstrual disorders has increased significantly. Exercise has been found to affect menstruation in a variety of ways, including inducing amenorrhea in athletes and perhaps alleviating symptoms of premenstrual syndrome and dysmenorrhea. Primary dysmenorrhea is characterized by a range of symptoms, foremost of which are lower abdominal pain that may radiate to the lower back or legs, headache, nausea, and vomiting. Some 75% to 85% of women experiencing dysmenorrhea report that their symptoms are mild, although dysmenorrhea may cause an appreciable number of absences from school and work. The symptoms are thought to stem from raised concentrations of prostaglandins, resulting in uterine contractions and ischemia. The origin of the increase in prostaglandins has not been decisively identified; one likely mechanism is thought to involve a decline in progesterone in the premenstrual phase, which results in the synthesis of prostaglandins in endometrial cells by membrane phospholipids. This theory is supported by the success of prostaglandin synthesis inhibitors in pain relief. As these inhibitors only provide pain relief in 70% to 75% of women, however, other factors are probably also involved. Possible contributors include deficient degradation of prostaglandins as the result of a defect in prostaglandin dehydrogenase, the vasoconstrictive action of antidiuretic hormone, and variations in pelvic blood flow, which may influence the synthesis or breakdown of prostaglandins. Primary dysmenorrhea affects between 47% and 80% of the general population depending on the age group studied; it tends to decrease with age and after pregnancy.[1]

Although exercise is generally thought to alleviate the discomfort associated with dysmenorrhea, the scientific literature on this phenomenon offers mixed evidence. One study identified a decline in the severity of symptoms after a 12-week aerobic training program,[2] and another reported diminished dysmenorrhea in exercising junior high school girls.[3] A number of studies have shown a correlation between life stress and gynecologic symptoms. Similarly, women who train intensively have been found to report fewer symptoms than women who exercise occasionally.[4] A number of other studies, however, have failed to find any relation between dysmenorrhea and levels of physical activity.[5-7] Furthermore, Metheny and Smith reported that after controlling for disposition and mood, exercise is actually associated with higher levels of menstrual discomfort.[8]

An interesting element of the relation between exercise and dysmenorrhea is the involvement of stress. A number of studies have shown a correlation between life stress and gynecological symptoms. Increased concentrations of cortisol have been associated with premenstrual syndrome,[9] and one study showed a correlation between menopausal symptoms and environmental stress.[10] Furthermore, dysmenorrhea has been treated successfully with stress reduction techniques.[11,12] Exercise is widely accepted as a means of moderating stress and stress-related symptoms; it may do this by reducing the perception of stress or inducing biochemical changes in the immune system.[13] A mechanism by which exercise may improve the symptoms of dysmenorrhea by reducing stress has been articulated by Gannon.[13] Menstrual pain probably stems from increased contraction of uterine muscle, which is innervated by the sympathetic nervous system. Stress tends to enhance sympathetic activity and may therefore increase menstrual pain by exacerbating uterine contraction. By relieving stress, exercise may decrease this sympathetic activity, thereby alleviating symptoms.

Because exercise has repeatedly been shown to improve mood, however, reduced dysmenorrhea may simply result from a better mood as opposed to an actual alleviation of physical symptoms. In fact, exercise is known to cause the release of endorphins, substances produced by the brain that raise the pain threshold. Many studies have failed to control for disposition and mood; the controlled study by Metheny and Smith suggests that although exercise may alleviate stress-induced dysmenorrhea, it may simultaneously aggravate symptoms.[8] One explanation

for this aggravation may be that exercise raises somatic awareness: regular exercise has been associated with increased sensitivity to bodily states. Alternatively, if women who exercise reduce their level of activity in the premenstrual phase, the resulting fall in endorphins could intensify dysmenorrhea.[8]

Overall, research into the relation between dysmenorrhea and exercise has been hampered by methodologic flaws such as varying definitions of dysmenorrhea and activity, different modes of data collection, disparate study designs, failure to perform blinded studies, and the retrospective reporting of symptoms. Blinded studies are particularly important in this area of research, as it has been shown that women may be influenced by previously held beliefs, taboos, and social expectations involving menstruation when answering questions about menstrual distress.[14] This complication, along with the confounding effects of stress, points to the variety of factors influencing dysmenorrhea and its relation to exercise. More carefully controlled longitudinal studies should help elucidate this complex relation. Research in this area is important, given the high prevalence of dysmenorrhea and the potential benefits of exercise.

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The virus and the hookworm

Hookworm infestation with the nemarode *Necator americanus* was endemic in the highlands of Sri Lanka during my internship there. Patients presented profoundly anemic with a characteristic facial appearance that often led to a "spot diagnosis." Indeed, it was common for an intern to tell a colleague in passing, "I see you've got another hookworm coming in."

Hepatitis A or infectious hepatitis, as it was known a few decades ago (to distinguish it from hepatitis B or serum hepatitis), was also a common infection. At any time, the medicine ward would include 3 or 4 patients so afflicted. As inspection of the urine was a better index of jaundice than examination of the eyes, clear glass jars containing a morning specimen of urine could be seen by each patient's bedside. Then, as now, the treatment was largely supportive. As "managed care" was a term yet to come, patients remained in bed for about 3 weeks, and when it was deemed that the patient had convalesced enough, plans for discharge were initiated.

When I was an intern, such a patient taught me a lesson that I shall never forget. Examination of the stools for parasitic ova and cysts was routine for all inpatients, regardless of the reason for admission. Helminthiasis was so prevalent that eradication of asymptomatic infestation was the usual practice. This particular patient's stool had yielded hookworm ova, and on the day before discharge, I ordered the standard dose of trichlorethylene. That was the treatment of the day and, although not as effective as the drugs now available, it had a high success rate in eliminating the parasite. Of course, a recurrence of illness was the rule rather than the exception. There was no way you could tell whether the recurrence was because of incomplete eradication or reinfection, nor did it matter.

On the morning of discharge, my patient was drowsy, and I rather naively attributed his somnolence to a poor night's sleep. The consultant was more impressed by the patient's appearance than by my explanation. He reached for the chart and studied it. "I see that you have prescribed TCE for this patient," he said.

Misinterpreting this as a compliment, I responded, "Yes, because his stools contained hookworm ova, and I thought it best to treat him before he left hospital."

"Do you know the formula for trichlorethylene?" he asked.

With increasing pride, I replied, "Yes, sir. C_2HCl_3."

"And what," he asked, "are the agents used for the experimental induction of hepatic necrosis?"

I still suspected nothing wrong. Remembering an old mnemonic from pathology, P for phosphorus that causes peripheral necrosis, and C for carbon tetrachloride that results in centrilobular necrosis, I answered with some satisfaction, "Phosphorus and carbon tetrachloride."

"And what," continued the consultant, "is the formula of carbon tetrachloride?"

That was when the penny dropped, as did my heart. As I responded, "CCl_4," I knew what was coming next.

"I hope you realize," he said, "that you have administered a highly hepatotoxic drug to a patient whose liver is recovering from hepatitis—a drug that is different by but two atoms from a powerful toxin." I said nothing; what could I say? Then he used the same phrase that had been used before in those circumstances: "Never again."

Results of the thymol flocculation and zinc turbidity—liver function tests used at the time—confirmed what we already knew: a marked deterioration. Fortunately, a few more days of tender loving care resulted in complete recovery. As I saw the patient walk out of the ward, I said to myself, "Never again."

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Med.Pix

Pattern recognition—shades of red

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QUESTIONS:

- In Figure 1, a 4-year-old girl with a fever and a red and swollen foot is brought to the clinic by her father. The girl cut her foot 3 days ago on a door. The redness and swelling can be seen in Figure 1 along with the area where the cut occurred near the 4th and 5th toes. On physical exam, the foot is warm, tender, red, and swollen, and the child's temperature is 103°F. What is your diagnosis?

- In Figure 2, this 66-year-old woman returns to the office after receiving a pneumococcal vaccine in the arm the previous day. Her arm is now warm, tender, red, and swollen. What is your diagnosis?

- In Figure 3, a 26-year-old man is seen with itchy red spots on his abdomen. He had been camping a few days earlier. Note the pustules and surrounding erythema. The area is slightly warm and tender. What is your diagnosis?

Figure 1

Figure 2

Figure 3

ANSWERS: Figure 1 shows a typical case of bacterial cellulitis. The initial cut in the skin was the portal of entry for the bacteria. The erythema is tracking up the foot and swelling is easily visible. The typical pattern of cellulitis with rubor, calor, tumor, and dolor is present.

Figure 2 shows a reaction to the pneumococcal vaccine. This looks visually just like the case of cellulitis and is a good example of how a visual pattern alone may be misleading or nonspecific. "Cellulitis" means inflammation of cells, but the term is typically used in reference to the skin, and generally meant to imply a bacterial infection of the dermis and subcutaneous tissues. The pneumococcal vaccine consists of 23 polysaccharides from 23 types of *Streptococcus pneumoniae*. Because there are no live bacteria in this vaccine, an infection cannot be the result of the vaccine components. This case represents an idiosyncratic reaction to the antigens in the vaccine. The history completes the pattern recognition for a vaccine reaction.

Figure 3 is most likely due to bug bites, although in this case, as is typical, the bug species was never identified. Central pustules and papules are surrounded by erythema. The inflammation of the skin producing the erythema is again not due to a bacterial infection, but rather to a reaction to the chemicals injected by the bug. Bug bites can become secondarily infected; usually such a case will have more crusting, but even more helpful is the history of a lesion that improves over time, only to worsen again after 2 or 3 days.

Pattern recognition in medical decision making

Pattern recognition is an essential technique in differential diagnosis. Experience and expertise in medicine consist in large part of a clinician's building a larger and more clearly delineated repertoire of recognizable patterns. In dermatology, pattern recognition depends primarily, but not exclusively, on visual patterns. Even in dermatology, data from the history and other parts of the physical examination contribute to pattern recognition.

Pattern recognition can also be misleading. When the diagnosis is not clear from the history and physical, we use hypothesis testing to collect additional data and increase the accuracy of our diagnosis. In these three cases, there are no useful laboratory tests that will confirm the hypotheses developed through pattern recognition. Therefore, hypothesis testing through laboratory examination was not a part of the diagnostic decision making in these cases.

Treatment

The young girl in Figure 1 was hospitalized for intravenous antibiotics. A first-generation cephalosporin was given to cover *Staphylococcus aureus* and *Streptococcus pyogenes*. The patient responded well to treatment and the cellulitis resolved.

The woman in Figure 2 was given oral Benadryl to treat her vaccine reaction. She also took oral acetaminophen for the pain, and her vaccine reaction resolved.

The young man in Figure 3 was given oral Benadryl for his bug bites. The lesions cleared fully.

Conclusion

These three cases illustrate the uses and limitations of pattern recognition in medical decision making. Pattern recognition is often the first step in making a medical diagnosis. Because it may be misleading at times, we must not make hasty decisions before all the data is collected. Looking at the arm in Figure 2 and not asking questions could easily lead to the misdiagnosis of cellulitis.

Lesions on the skin come in all shades of red. It is the job of the astute clinician to be able to recognize the diagnosis among these varying shades.

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Note: If the patient's identity is recognizable, a signed permission form should accompany the submission materials.

Culture and Medicine

Dutch euthanasia: could it happen here?

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Dr. Vander Veer is a general surgeon in Phoenix, AZ. In 1998, he visited the Netherlands to study their system of care at the end of life. In this article, he shares his observations of the Dutch system and its relevance to the United States.

I see many cancer patients in my practice and have always followed them, particularly if they have advanced-stage disease, so I have experienced carrying patients and their families through the dying process. I have seen how poorly our society deals with death and dying in general. Most doctors, too, do not deal well with it, perhaps because we're so highly specialized in this country, and our care is so fragmented.

In 1995, at a bioethics conference in London, I heard a panel discussion about end-of-life care in which Dame Cecily Saunders (founder of the hospice movement) and Dr. Pieter Admiraal (an advocate of Dutch euthanasia) were speakers. I was familiar with hospice and endorsed it, but unfamiliar with the Dutch system, although I had read about it. Because I have a niece in Delft, I decided to go see for myself. I wrote to Admiraal, who was to be out of the country at the time of my visit but put me in touch with several helpful individuals. I stayed in Delft and arranged interviews with key people in The Hague and Amsterdam.

Learning from the literature

While reviewing my teaching file, I was surprised to find 50 articles on euthanasia or physician-assisted suicide. Most helpful were several monographs, including a recently published volume called Euthanasia and Law in the Netherlands,[1] written by an American who had immigrated to the Netherlands 17 years earlier. A second volume entitled The Low Sky[2] was less scholarly but gave the flavor of Dutch society. A third valuable work by a Dutch psychiatrist[3] was influential in the evolution of the Dutch system.

The legal position in the Netherlands

Under the Dutch penal code, both euthanasia and physician-assisted suicide are illegal. If convicted, a physician can face a stiff fine and imprisonment. Special provisions are made for physicians, however, if they follow guidelines established by the Royal Dutch Medical Association (KNMG), and if they report the case as one of euthanasia or physician-assisted suicide and not natural death. The issue of reporting has become the Achilles' heel of the system, for many cases go unreported and therefore cannot be reviewed. A special commission (the Remmelink Commission) set up by the Dutch government granted confidentiality and immunity to 400 physicians and interviewed them to establish the prevalence of the practices of euthanasia and physician-assisted suicide.[4] The Remmelink Commission found that these practices account for about 4% of Dutch deaths annually, with euthanasia 6 times as common as physician-assisted suicide. The interviews revealed that at best only about half of the cases are reported. The three most common reasons given for not reporting were (1) the process is unwieldy (it requires filling out a 51-item questionnaire); (2) if the patient is near death from a terminal disease, many doctors just sign the case out as a natural death to avoid an investigation; and (3) many physicians objected to the criminal overtones of the reporting system, including interrogation of a grieving family by police.

How the Dutch system evolved

The Dutch system evolved over thirty years, beginning in about 1966, when there was a Dutch case similar to our Karen Quinlan case involving a woman in a coma on life support. When the anesthesiologist decided unilaterally to turn off the respirator, the father lodged a complaint with the Medical Disciplinary Tribunal (like our Board of Medical Examiners). The case went through the court system. The court mandated that in such situations colleagues must be consulted and the family must be involved. The doctor was sanctioned and the case provoked much discussion.

Three years later psychiatrist J.H. van den Berg published the small but provocative volume Medical Power and Medical Ethics.[3] This book was widely discussed. It went through 21 printings in 7 years and had a great impact on end-of-life care. Van den Berg divided the history of medical technology into three periods: (1) medical powerlessness (when doctors had few options); (2) a transition period; and (3) the current era of medico-technological power, which began in about 1965. Whereas when doctors were powerless, their duty was to preserve, spare, and prolong human life wherever and

whenever possible, now a new ethic was required, van den Berg submitted, one in which the new power—the power to preserve and sustain life—is to be used sensibly. Otherwise, he asserted, we create monsters. In the book he presents 14 cases, terrible triumphs of our technology. Two such cases—a baby with congenital malformations due to thalidomide and a person who is paraplegic and has had a hemicorporectomy—are shown in shocking photographs. One criticism of van den Berg is his apparent willingness to write off patients with such disabilities. (It seems ironic that in his photographs, the baby and the person with paraplegia are smiling into the camera.) The book is hard-hitting, even in the English translation of 1978. It was discussed widely in Dutch coffeehouses, and it influenced thinking about technology, terminal care, and the ethical issues they raised.

At about that time in the Netherlands, the issue of abortion was being discussed. It produced a schism in the Royal Dutch Medical Association, where a group split off to form the pro-life Dutch Association of Physicians. A few years later, when euthanasia began to be talked about, the leaders of the KNMG, seeking to avoid another split, at first took no position on it, then issued guidelines for its conduct, and thus kept euthanasia within the province of the medical profession.

The 1975, a working group of the KNMG defined euthanasia as acts or omissions intended to cause a patient's death, in his or her interest, which could only be undertaken if voluntarily requested by a patient who has no hope of recovery. Such cases should be discussed with a colleague, the KNMG recommended, and usually a passive method (such as withdrawing or withholding care) would be most appropriate. The group did acknowledge that there were rare circumstances where active measures might be used to end prolonged suffering that could not be relieved in any other way. Within a decade, after several other euthanasia cases had been adjudicated, the KNMG offered five "requirements of careful practice" which would make euthanasia acceptable when practiced by a physician. The request must be voluntary; it must be well considered; the desire of the patient must be lasting; the suffering must be unbearable, with no alternatives for relief; and the doctor must consult a colleague. In 1992, a sixth requirement was added: the physician must keep a written record.

Court cases

A series of court cases from 1969 to the 1990s gradually established the parameters under which euthanasia and physician-assisted suicide could be carried out in the Netherlands, with an agreement reached between the government and the physicians. Griffiths et al.[1] give an excellent account of these cases in their monograph.

AP Photo/Hans Deryk

The president of the Euthanasia Research and Guidance Organization, Derek Humphrey (who has been active in Oregon), in a heated discussion with an opponent of assisted suicide, Dr. Ira Byock.

Physician-assisted suicide is not done in hospitals, always at home, and is one sixth as common as euthanasia. It is done with a lethal dose of a barbiturate, usually, or a cocktail of drugs. Euthanasia is performed by giving an intravenous injection of a sedative, followed by curare or a similar drug. One person I interviewed, a counselor with the euthanasia team at Dr. Admiraal's hospital in Delft, had a husband who chose physician-assisted suicide when he was dying of prostate cancer. She said he was a stubborn man who said his goodbyes to family and friends, then summoned his physician for the final act. She was not in favor of it because at the end he was weak and shaky. He

AP/KEYT-TV

Rebecca Badger gives a television interview in California two days before Jack Kervorkian helped her commit suicide. Badger had multiple sclerosis.

spilled some of the lethal drink down his beard as he took the dose, but he died peacefully 2 hours later at home.

Dutch society in contrast with the United States

The Netherlands is a relatively cohesive and uniform society. The population is 96% white. It is liberal and characterized by freedom of conscience and tolerance of diversity. Change is accomplished politically by consensus, coalition, and conciliation. Unlike America, it is not an especially violent society.

The strongest church in the country is the Dutch Reformed Church, and the influence of the Catholics and the Evangelical Christians is far less than in the United States: there is no Moral Majority or Christian Coalition in the Netherlands. Early on, the Dutch Reformed Church endorsed abstaining from life-prolonging measures in terminal care (passive euthanasia) in situations of hopelessness.

Almost all the population is covered by medical insurance and all people are covered for catastrophic illness. Medical malpractice lawsuits in the Netherlands are almost nonexistent: the Dutch trust their physicians, and most Dutch families have *huisarts,* general practitioners, who live nearby and often have their offices in their homes. (One study showed that 17% of the *huisart's* patient contacts were house calls.) The Dutch have up-to-date medical care, but the system is oriented around the primary physician and is not nearly so specialty-oriented as in the United States.

Another important contrast is the approach to end-of-life care. In the Netherlands, there are five accepted medical behaviors that can shorten life: (1) withdrawing care in situations of futility (as determined by the physician); (2) treating terminal symptoms vigorously (even though it may shorten life); (3) withdrawing care at a patient's request; (4) physician-assisted suicide; and (5) euthanasia. These approaches to treatment are accepted as good medical care. The Dutch (as a society, and Dutch physicians, too) are much more realistic about death than we are. For example, the situation—not rare in the United States—where a relative arrives from out of town at the bedside of a dying patient and insists that everything be done is rare in the Netherlands. About 40% of Dutch patients die at home, whereas in the United States the proportion is 15%. The Dutch have high-technology care available in their hospitals, but they do not use it to the extent that we do, because death is not denied so vigorously in their culture as it is in the United States.

Abuses in the system

The Remmelink Commission established that there were about 1000 cases of euthanasia each year that were not voluntary. In 86% of those cases the patient was terminally ill and expected to live for only a few days. Usually euthanasia had been discussed with the patient, but a formal request had not been made. One of the investigators I interviewed (an academician who had been a general practitioner and who has published several papers on the Dutch system in The New England Journal of Medicine) said, "If a decision has been made to withdraw care in a terminal case, it is a very small step to performing euthanasia to relieve suffering at the end, for the average Dutch family physician."

The new law in Oregon

It is unlikely that the United States will ever endorse euthanasia as has been done in the Netherlands because of the contrasts, already noted, between the two societies. The US Supreme Court left the decision up to "the laboratory of the states," and the experiment is being conducted in Oregon now. But Oregon's physician-assisted suicide is different from that in the Netherlands. In Oregon the doctor does not need to be present when the lethal dose is taken, but in Holland the doctor must be there. That in itself may say something about death and the doctor/patient relationship in the two countries.

Oregon does have safeguards designed to detect patients with depression. The AMA's program of Education of Physicians in End-of-Life Care could be a major step toward improving palliative care in this country. Other states are likely to try physician-assisted suicide, but it seems unlikely that euthanasia will ever be openly endorsed. Dr. Jack Kevorkian has now been sanctioned for performing euthanasia. This action, and the passage of physician-assisted suicide initiatives, are effectively issuing a wake-up call to American medicine to improve terminal care. It's long overdue.

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capsule

Death toll high in Alaskan fishermen Eleven years ago the US government passed an act forcing commercial fishing boats to carry safety, survival, and fire fighting equipment. Since then the death toll in Alaskan fishermen has almost halved (Occupational and Environmental Medicine 1999;56:691-695). Fishing in Alaskan waters remains extremely dangerous, however, particularly for crab fishermen, who must harvest their catch in rough winter weather from the freezing Bering sea. Over 60 Alaskan crab fishermen have drowned since 1991, a yearly occupational death rate of 275 per 100,000.

The historical feud over polio vaccine: how could a killed vaccine contain a natural disease?

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Summary points

- The Salk killed-virus polio vaccine, developed in 1953 and field-tested the following year under the sponsorship of the National Foundation for Infantile Paralysis, faced great opposition from virologists, including the Foundation's own advisors.
- The controversy over the Salk vaccine appeared to be a debate over the risks and benefits of killed-virus versus live-virus vaccines, with attendant criticism of the publicity surrounding the vaccine's introduction.
- The deeper conflict between advocates and opponents of the Salk vaccine was between two models of biomedical research.
- Salk and his supporters understood viral infection and immunologic response as mechanistic processes, which could be replicated and manipulated by laboratory methods.
- Salk's opponents described viral research as the controlled observation of life processes, to further understand those processes for clinical application.

"How dare I claim that the world is round, not flat?" a beleaguered Jonas Salk protested to his biographer, Richard Carter, in the early 1960s.[1] Salk usually argued in more technical terms, yet his frustration over scientific attacks on his inactivated ("killed") virus polio vaccine was evident. The February 1997 decision of the US Advisory Committee on Immunization Practices to recommend increased reliance on inactivated polio virus—designed to reduce the incidence of vaccine-associated polio linked to Albert Sabin's oral live-virus vaccine—marked the end of four decades of controversy and represented a partial vindication of Salk and his sponsors, the National Foundation for Infantile Paralysis.[2] In June this year a federal advisory panel went further, recommending that the United States abandon the oral vaccine, a recommendation expected to be accepted by the Centers for Disease Control and Prevention.

In recent years Salk and Sabin, and their supporters, have couched the debate in the language of cellular and genetic immunology. Historical accounts of their rivalry have often cited the intense publicity that surrounded the introduction of Salk's vaccine as the reason for its long disfavor among scientists.[3] In 1953, however, lacking present-day understanding of antibody formation, virologists debated the vaccine question instead in terms of the nature and meaning of biomedical research.

Jonas Salk first presented his work to the National Foundation's Advisory Committee on Immunization on 23 January 1953 in Hershey, Pennsylvania. He was then 39 years old, the committee's youngest member. Since completing his residency, he had been supported by National Foundation grants, first working with Thomas Francis at the University of Michigan, then in his own lab in Pittsburgh, where he had spent several tedious years on the "scut work" of typing strains of poliovirus.[4] He had developed an exacting multistep process of inactivating the three known strains with formalin and combining them in a "killed-virus" vaccine. During 1951 and 1952, he had tested this preparation on 161 children who lived in institutions. The children had shown no ill effects, and their antibody titers had risen significantly.[4]

Several committee members were impressed with Salk's presentation and recommended scheduling a field trial of his vaccine. But virologist John Enders, a Nobel laureate, advised a more deliberate strategy: "I would suggest more experimentation along the lines that he is doing so admirably at the moment, and not enter into a large experiment which will inevitably be connected with a lot of publicity and may jeopardize the entire program." Albert Sabin of the University of Cincinnati, who was attempting to develop a live-virus vaccine, supported Enders.[4,5]

National Library of Medicine

Jonas Salk vaccinating a child

Sabin referred to the events that followed as "the mess after Hershey."[6] Within a week, the foundation held a press conference, promising field-testing of a polio vaccine within a year, then followed the press conference with a flurry of publicity releases.[7,8] On 25 May, Thomas Rivers of Rockefeller Hospital, dean of the foundation's scientific advisors, created a new Vaccine Advisory Committee to supervise the planned trials. Only two virologists from the Committee on Immunization were asked to serve; the rest of the members of this new group were specialists in public health or internal medicine.[4]

Clearly, Rivers and the foundation had determined, soon after hearing of Salk's initial results, to move ahead with a field trial, to draw support from public opinion and the general medical community, and to remove or neutralize the opposition of some virus experts. In the latter objective they hardly succeeded, in that criticisms of the Salk vaccine persisted even after the success of the 1954 trials. Some critics attacked the high-handed usurpation of scientific prerogative by a lay volunteer group and the amount of publicity about the vaccine. But Enders, Sabin, and their colleagues directed their fire at the scientific deficiencies of the Salk vaccine. They asserted the superiority of an attenuated vaccine, as in the cowpox/smallpox model, one without sufficient virulence to produce paralytic disease but potent enough to stimulate permanent immunity.

The relationship between antibody and resistance

Salk did not dispute the rationale behind a live-virus vaccine, but he did challenge its preeminence as a model. Ten years of work had led him to "the now reasonable assumption that the relationship between antibody and resistance is more than one of mere association—that it is one of cause and effect," and to the related belief that antibodies seen in the blood of persons who had recovered from a disease were not merely by-products of infection but indeed the agents of subsequent immunity.[9] He had demonstrated experimentally that "poliomyelitis virus is a relatively potent antigen," one that generated high antibody levels and, he contended, effective immunity.[10]

The problem was to stimulate antibody production without running the risk of paralysis or death; as the solution, Salk proposed a highly antigenic strain of poliovirus, inactivated under very specific conditions of time, heat, formalin concentration, and acidity. He argued that his precise and painstakingly developed specifications guaranteed that the virus would not be lethal.[11]

Salk's experiments with monkeys, and later with children, had shown that his process generated a safe vaccine, and one that would produce the antibody levels that he equated with immunity. The question remained whether the postulated immunity would endure throughout life. While the debate raged during 1953, he continued his tests, demonstrating that a child once vaccinated reacted to a second injection with even higher antibody titers; this booster effect, Salk thought, ensured that any subsequent infection with the natural virus would be met with a horde of antibody; therefore, immunity from a killed virus would be lasting.[9-11]

He had been cautious in presenting his early results, hesitant to consider a large field trial; but in March 1953, he was already confident of his method and his vaccine.[4] He became increasingly dismayed as he found that "the idea of a live-virus vaccine has exerted, and still does exert, a very powerful influence, and one that seems to determine not only attitudes and opinions, but policy for action as well"—although, since no attenuated virus that could be safely and effectively used for vaccination had been found, "there has been not much to discuss except the idea."[10]

Salk recalled to Richard Carter some years later: "What had once been skepticism about attempts to develop an effective killed vaccine was now becoming ideological conflict. How could a killed vaccine contain the magical life force of the natural disease?"[1]

An ideological conflict

Salk's former mentor, Thomas Francis, who directed the field trials, had described the ideological conflict more dispassionately in 1955: "The two outlooks, then, are simply this: inactive virus vaccine is apparently a test of the straightforward hypothesis that antibody induced by the administration of antigen can provide protection without subjecting the recipient to harmful effects of even the inapparent infection. The other, through the use of modified active virus, seeks to induce antibody formation, but wishes to add some undesignated advantage derived from apparently harmless infection."[12]

What were the advantages attributed to live-virus vaccine?

Albert Sabin, a Polish emigré only eight years older than Salk, had worked with polio cultures since the 1930s. In 1953, with National Foundation support, he was attempting to isolate an attenuated virus by identifying the least active viruses in a tissue culture, reculturing these, then repeating the process with each successive generation. There may have been a degree of self-interest in his critique of the Salk vaccine, but he was strongly seconded by Enders, Herald Cox (who had worked with live virus at Lederle Laboratories), and others of weight and reputation.

In June 1953, Sabin opened a presentation at an American Medical Association meeting by saying, "Since there is an impression that a practicable vaccine for poliomyelitis is either at hand or immediately around the corner, it may be best to start this discussion with the statement that such a vaccine is not now at hand and that one can only guess as to what is around the corner."[13]

He denied Salk's assumption that antibody production was equivalent to immunity, contending that certain

Albert Sabin

immunity could exist only in an individual who had survived actual infection; and he expressed concern about the safety of the highly antigenic strains used in killed-virus.

Finally, Sabin argued that the Salk vaccine might "interfere with the subclinical infections which under natural conditions immunize the vast majority of the population against poliomyelitis." His conclusion was that, although a safe killed-virus vaccine, if one were possible, might be used as a temporary preventive, "the ultimate goal for the prevention of poliomyelitis is immunization with 'living' avirulent virus, which will confer immunity for many years or for life."[13]

Herald Cox had voiced similar thoughts in April: "I am of the opinion that the most logical and practical way to immunize infants and children against poliomyelitis is to follow the pattern that seems to take place so universally under natural conditions…"[14]

Likewise John Enders had written: "The ideal immunizing agent against any virus infection should consist of a living agent exhibiting a degree of virulence so low that it may be inoculated without risk. Since a decline in the virulence of other viruses has in the past frequently occurred after prolonged cultivation in vitro, one might expect this change also to take place in the agents of poliomyelitis."[15]

The issues of immediate immunity and safety would be resolved by the actual experience of the field trials. But the concept that only a natural infection with a living agent, resembling the actual disease, could confer real immunity could not be addressed with the knowledge and methods available in 1953.

The underlying conflict here is between two concepts of biomedical research. In the Sabin-Enders model, the scientist observes the living organism and describes its natural history and behavior, which may be verified experimentally and then applied to human advantage. In the Salk process, the researcher uses scientific methods, not to observe but to manipulate, changing the organism in a non-natural way and altering the normal course of events. Both models have long antecedents in the history of biology, the former analogous to studies of anatomy and evolution, the latter to "mechanistic conceptions" such as that of Jacques Loeb.[16]

Salk and Francis accused their opponents of a belief in some special quality of the living virus that could not be reduced to physical actions and interactions, a vitalism considered passé in the 1950s.[17]

But the foundation's own research program prior to 1953 had emphasized scientific knowledge of the disease entity over vaccine production. The logical next step for most virologists was the painstaking cultivation and observation of live virus, while small trials using the killed virus gave information about antibody protection and persistence. Ultimately, such patience and rigor should result in the best therapeutic solution. The rapid shift to large-scale vaccine production and testing seemed to many an abandonment of science for technology.

In an era when scientists have developed such an impressive tool kit for manipulation of the most basic molecules of life, and when lucrative patents and public acclaim await their application, it may be worthwhile to review this debate again.

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News and Features

Right-to-die bills defeated in more than 28 states

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AP Photo/Ron Edmonds

Gregory Dugan of Washington protests outside the Supreme Court against physician-assisted suicide.

When the people of Oregon voted to legalize physician-assisted suicide a year ago, the executive director of the advocacy group Compassion in Dying hailed it as a turning point for the death with dignity movement. But the overwhelming defeat of similar initiatives in other states has stopped those hopes dead in their tracks. Although bills to legalize physician-assisted suicide have been debated in California, New York, Michigan, Arizona, Connecticut, Louisiana, New Hampshire, and Florida, none has passed, nor are any expected to.

In Michigan, voters recently rejected Proposal B, a measure for assisted suicide, by a margin of 71% to 29%. Under this proposal, Michigan residents or, in some situations, their out-of-state relatives would be eligible for assisted suicide if confirmed by one psychiatrist to be mentally competent and by two physicians to be terminally ill with 6 months or less to live. After meeting these criteria, these individuals would be allowed a lethal dose of medication to end their lives. Proponents of Proposal B contend that 30 groups opposed the measure, including the Catholic Conference, Right to Life, the state medical society, the state hospice association, and a pressure group for disabled people. The bill, they argued, was defeated by these well-funded special interest groups and not because of a lack of popular support.

Similarly, in California, a bill to allow physician-assisted suicide (AB 1592) was jammed through a state assembly appropriations committee only to be tabled once it reached the assembly floor. The bill—modeled after an Oregon law that allows a physician to prescribe a lethal dose of medication to a terminally ill patient—will not be voted on until next year. Meanwhile, in New York, some members of the New York Task Force on Life and the Law regarded assisted suicide as ethically acceptable in exceptional cases, yet all 24 task force members concluded that "constructing an ideal or 'good' case is not sufficient for public policy if it does not reflect medical practice." Many task force members were deeply moved by some patients' suffering, but they felt that giving publicly sanctioned suicide assistance to those patients endangered a much larger number of vulnerable people. In Arizona, a similar bill proposed by Peter Goudinoff (D-Tucson), then the state's senate majority leader, would have legalized doctor-assisted suicide. The bill was defeated in the state legislature 3 years ago.

During the past 2 years, in more than 28 states, no bill proposing the legalization of physician-assisted suicide has been successful, according to the National Conference of State Legislatures. Three states—Michigan, South Carolina, and Virginia—even took the extra step of passing new bans on the practice. In total, at least 45 states have outlawed physician-assisted suicide.

Oregon appears to be the striking exception to this trend, having passed a bill that allows physician-prescribed lethal medication for terminally ill patients. Opponents of the bill argued that it passed overwhelmingly due to voter resentment, since the state legislature forced a second vote on the issue after it had already been approved by a 51% to 49% margin—the first time in state history the legislature tried to repeal a voter-passed initiative. Last year in Oregon, 15 people used their right to physician-assisted suicide.

There are signs, however, that the tide against assisted suicide measures may have reached an ebb. The Supreme Court ruled in 1997 that people do not have the constitutional right to suicide or dying but left the question of outlawing physician-assisted suicide to the individual states. A class-action federal lawsuit filed in Detroit on 19 March 1999, if successful, would establish federal protection of the constitutional right to be free from unbearable and irremediable suffering due to a medical condition. Such a right would allow physician-assisted suicide and would protect doctors from prosecution.

"The fact that 45 states have banned physician-assisted suicide does not necessarily represent an accurate barometer of public sentiment," said University of Pennsylvania bioethics professor Glenn McGee. "Public opinion polls are subject to sudden changes when it comes to this issue."

Most of the bills proposed to date have been modeled after Oregon's successful initiative. To qualify under the California measure, for example, according to Dion Aroner (D-Berkeley), the state assembly woman who

proposed the measure on behalf of Americans for Death with Dignity, a sick person must have received a medical diagnosis saying that he or she is within 6 months of death, must voluntarily request assistance in dying, and must enlist two doctors to review the case. In addition, the California measure requires that a request for assistance be made twice, at least once in writing. If doctors question the competence of a patient, they can seek a psychiatric examination.

The high profile of these measures may produce general benefits for terminally ill patients. "Time after time, actions to ban assisted suicide or to reaffirm existing bans have been followed by advances and improvements in pain control," said Richard Doerflinger, Associate Director for Policy Development for the National Conference of Catholic Bishops. "When Rhode Island considered a new ban on assisted suicide in 1996, the state medical society objected that such a ban would have an adverse effect on physicians' willingness to use drugs like morphine for aggressive pain control. But, in fact, the opposite happened. In the year following enactment of the ban, according to official figures from the Drug Enforcement Agency, Rhode Island more than doubled its per capita use of morphine for pain control, rising from 46th among the states to 19th in morphine use."

Euthanasia allowed in Dutch patient with dementia

see also p.268

Tony Sheldon, Utrecht

AP Photo/ Carl D. Walsh

Emile van Eeghen of Maine, a supporter of physician-assisted suicide whose father died from this method in the Netherlands

A physician in the Netherlands has escaped prosecution after helping an elderly patient with vascular dementia to die. In the first public case involving a patient with dementia, the patient was considered to have been competent to request assisted suicide, and the procedure was judged to be medically and legally sound.

The facts were reported in a case history in a Dutch medical journal (Nederlands Tijdschrift Voor Geneeskunde 1999;143: 17). Dutch law states that doctors can avoid prosecution for assisted suicide only if their patient has persistently made an informed and voluntary request and is suffering unbearably and hopelessly. The patient in this case was considered "ill enough not to want to go on anymore, but...not so demented that he could not decide."

A complex protocol, the first of its kind in the Netherlands, was set up by the hospital involved, the Twents Psychiatric Hospital, to consider the patient's request. The case involved a 71-year-old man who had been diagnosed 4 years ago as having cerebral atrophy and multi-infarct dementia. Magnetic resonance imaging confirmed that his condition was deteriorating. He asked his doctor to help him to die because he did not want to cope with a further deterioration in his condition.

The patient's case was assessed by the hospital's chief psychiatrist, a committee of independent professionals, and an external psychiatrist. Four months after assessment, the patient died at home after drinking a high-dose solution of barbiturate given to him by his doctor. The public prosecutor approved the procedure after consultation with the national forum of procurators general.

The case has raised fears that it brings euthanasia for elderly patients with dementia a step closer. The Alzheimer's Foundation in the Netherlands warned: "Dementia itself could never be a reason for assisted suicide because the patient is incapable of making an informed request."

The doctor involved in the case defended her actions, writing in the journal that she opposes euthanasia and assisted suicide for patients who are unable to express their will, and she agrees that most patients with dementia cannot. In this case, however, her patient was lucid at all times and able to understand the consequences of his request.

Medical director of the Royal Dutch Medical Association, Rob Dillmann, said that if a patient was in the early stages of dementia with an untreatable progressive neurological disease, but still clearly competent, then there was the possibility that physician-assisted suicide could be appropriate.

Medicine and Money

Academic health centers: a future of struggles and new identities

see also p.221

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Last year, the University of Pennsylvania's health services system lost nearly $90 million. Georgetown University Medical Center has lost almost $120 million in the past two years. Even after sharp cost-cutting, Brigham and Women's Hospital in Boston, a chief training ground for Harvard Medical School, lost $15 million in the first quarter of this year.[1]

Academic health centers have been among the nation's most successful institutions, making headlines for advancing scientific knowledge, developing and providing dramatic new forms of patient care, and training an ever-increasing cohort of new health professionals.[2] But they now experience challenges that have put their traditional missions in some jeopardy,[3] challenges that include decreased government support for operations and research, more managed and cost-conscious healthcare reimbursements, and increased competition from medical practices, hospitals, and nonuniversity research operations.[4]

The losses cited above were all reported in the Chronicle of Higher Education, demonstrating that academic health centers and their financial crises are in the headlines. Many blame the financial situation on inadequate institutional responses to changes in healthcare delivery and education. One response of academic health centers has been to redefine traditional relationships with the care delivery system by negotiating partnerships with health systems, both for profit and not for profit, that offer a range of services and a more secure fiscal base. Academic health centers have negotiated "partnerships" such as buyouts, mergers, affiliations, and lease agreements. The arrangements are as varied as the academic health centers themselves. Their structure is influenced by such forces as managed care penetration and market competition (including competition from other academic health centers nearby); fallout from the 1997 Balanced Budget Amendment; and the unique features of each academic health center, including institutional history, culture, and key individuals in leadership positions.

The Center for the Health Professions at the University of California, San Francisco, conducted an exploratory study of three academic health centers in 1998 to examine the impact of such partnerships on teaching and research missions. The stories of two of them, the Allegheny University of the Health Sciences in Philadelphia and the University of Minnesota in Minneapolis, offer contrasting scenarios of how things have changed and lessons in how the future might unfold. These stories underscore the dramatic issues that arise when different cultures merge and a new market-based approach to healthcare delivery, research, and education is adopted. Together, the stories suggest a pressing need for a new social vision of the nation's academic health centers.

Summary points

- Academic health centers are creating partnerships with health systems in response to their financial crises.
- These partnerships lead to cultural shifts at academic health centers and increase fiscal awareness and accountability for education, research, and patient care.
- In the future, more academic health centers are likely to develop partnerships, which may lead to a fundamental redefinition of their missions and identities.
- Transformation will involve creating a new social vision and role for academic health centers in the changing healthcare system.

Allegheny University of the Health Sciences

Allegheny University of the Health Sciences began to take shape in 1987, when Allegheny General Hospital in Pittsburgh, Pennsylvania, acquired the financially struggling Medical College of Pennsylvania. The medical school needed a fiscal partner to survive in a marketplace with excess bed capacity, declining reimbursements, and fierce competition from local academic health centers. The hospital, in turn, was looking to enhance its academic and research cachet and, ultimately, its competitive edge. Less than a decade later, the Medical College of Pennsylvania was part of a conglomerate run by the Allegheny Health, Education and Research Foundation (AHERF), which by then had acquired another Philadelphia medical school, namely Hahnemann University, a health professions school, amounting to the largest network of hospitals and health systems in the state. Allegheny University of the Health Sciences, itself owned by the private, not-for-profit AHERF system, housed Medical College of Pennsylvania/Hahnemann, one of the largest medical schools in the country, and sponsored a range of other health professions education programs.

AHERF's acquisition of the medical schools, their respective university hospitals, and subsequently, several affiliated hospitals in the region, was motivated by its desire to increase access to tertiary care, research dollars, and prestige, and to establish a statewide integrated network of healthcare delivery. AHERF brought its corporate archetype to bear on how education and research were structured within the academic health center. Departments became independent business units, while faculty practices, previously managed by individual departments, were merged to achieve economies of scale, control, and bargaining strength in numbers. Allegheny University of the Health Sciences profited from an infusion of money, which

was used to expand the faculty, to fund research (leading to a dramatic rise in the university's NIH ranking), and to create a new school of public health.

In expanding its network, AHERF found itself having to acquire hospitals that were part of larger systems. For example, in acquiring St. Christopher's Hospital for Children in Philadelphia, to ensure access to pediatric specialty care, AHERF was encumbered with three struggling affiliated community hospitals. After several years of expansion, fueled by aggressive infusion of capital, a number of forces converged to strain AHERF's burgeoning system. By 1997 the system was losing nearly $1 million a day. Measures to cut costs were instituted to stem the rising tide of red ink, but they provided too little relief too late. In 1998 the newly chartered Allegheny University of the Health Sciences, its medical school, and affiliated Philadelphia hospitals were in the midst of bankruptcy proceedings.

AHERF's problems went much deeper than declining reimbursements and the growing impact of cost-conscious, managed-care insurance plans. Forty million dollars in new faculty costs had been incurred in less than three years, and a system still driven by the need to fill hospital beds was struggling with an occupancy rate of 60%. Other contributing factors included mismanagement at the top levels of the organization, uncontrolled desire to grow at any cost, and financial misconduct. According to a report in the Association of American Medical Colleges Short, Topical, and Timely News, on 28 June 1999, Allegheny's creditors filed suit, seeking more than $1 billion in damages, against the Allegheny Health Education and Research Foundation, five former AHERF officers and directors, and five current officers and directors of Allegheny University Hospitals-West. The creditors reserve the right to add additional defendants as the case proceeds. Among other things, creditors accused AHERF officials of lax oversight and failure to implement cost controls.[5]

Tenet Healthcare Corporation has purchased eight of AHERF's Philadelphia hospitals, the faculty practices, medical schools, and Allegheny University of the Health Sciences for $345 million. Tenet has agreed to provide $33 million in each of the next three years for administration, supervision, and teaching provided by the AHC faculty to the hospitals. Drexel University has agreed to take over management of Allegheny University of the Health Sciences, and officials are optimistic that this outcome will preserve the educational, research, and service programs of the institution.[6]

AP Photo/ Carl D. Walsh

It can be hard to balance health care and cost.

University of Minnesota

The University of Minnesota's academic health center, one of two in the state and the only one that is publicly funded, consists of six professional schools, which train nearly 80% of the state's health professionals. Minnesota, where managed care took root, is known for its highly competitive healthcare environment and consolidated integrated delivery organizations. In the early 1990s, the University of Minnesota began to experience increasing financial hardship, caused by a shift of care to ambulatory settings and by the health center's competitive disadvantage in managed-care contracts, due to the higher costs of providing care associated with teaching and research. In 1997, the hospital posted a deficit of $20 million, owing to a decline in both patients and revenue. It was projected to have a deficit of $100 million by 1999.

Faced with either closing or selling the hospital, the University of Minnesota looked for a partner to provide financial solvency, to support its academic programs, and to guarantee continued service delivery. In 1997 the academic health center sold its hospital, affiliated outpatient clinics, and parking sites to Fairview—a private, not-for-profit health system—for $87 million. Fairview expanded its capacity for tertiary and quaternary care and agreed to provide resources to support education and research, as well as opportunities for outreach education and research, throughout the system. The agreement allowed the academic health center and Fairview to function collaboratively while retaining their respective autonomy, authority, and governance.

As in the Allegheny University of the Health Sciences scenario, Fairview established a new payment and accounting system and pushed the health center to improve its accounting of and accountability for the costs associated with education, research, and patient care. In the process, the University of Minnesota agreed to reduce the annual subsidy it drew from the hospital, dropping from $53 million to $12 million.

As in the Allegheny University of the Health Sciences scenario once again, the University of Minnesota was forced to adopt a corporate model of doing business, becoming more fiscally aware and expecting faculty to become more aware and accountable—a major cultural shift for the academic health center. On the other hand, the amount of capital infusion from Fairview to the University of Minnesota was substantially smaller than that received by Allegheny University of the Health Sciences. The University of Minnesota did not expand its faculty, create a new professional school, or shore up its NIH research ranking.

The Fairview-University of Minnesota partnership, now in its second year, has achieved its primary goal: the survival of the academic health center. Further results of the process continue to develop: defining education and research costs, integrating clinical efforts across two very different systems, incorporating training and education into the new system, and adapting to the challenges of merging cultures and priorities.

New identities in the future

Having lost their position at the pinnacle of the healthcare system,[7] academic health centers are struggling for their identity. As these two examples show, academic health centers must become more accountable for determining and supporting the costs of education and research without relying on substantial subsidies from clinical revenue. Institutions that continue to be successful in their traditional missions are likely to be faced with developing novel arrangements, such as affiliating with an external health system partner.

Academic health centers also need to create a new social vision of their role, responding to the ever-evolving healthcare system and to the needs of the community and society they serve. The new role must involve educating health professionals for practice in contemporary systems and conducting biomedical and health services research. Some academic health centers will make fundamental contributions in more than one area, while others may find a specific focus to be a virtue, especially when the focus clearly responds to interests of the external partner. It is highly likely that a greater range of missions and greater institutional distinctiveness will be a hallmark of academic health centers in the future.

The capacity of academic health centers to sustain a trifold mission—to teach, conduct research, and provide clinical care—has depended on revenue from fee-for-service and uncapped Medicare reimbursements and on the ability to cross-subsidize activities. Without strict accountability, large institutions have been built and are now faced with the difficulty of sustaining multiple missions in a very cost-conscious environment.

A number of questions are increasingly being asked of academic health centers. What do the healthcare system and the larger society require from academic health centers, and what are the most effective ways to meet these needs? At the crux of the answers to these questions cannot simply be the need to ensure the survival of academic health centers as we know them.[7] If survival is the most significant driver, it is doubtful that academic health centers will create a sustainable future for themselves, for the organizations that advance them, or for the communities that they serve.

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One hundred years ago

In an excerpt from the Transactions of the Medical Society of California, 1898, J.W. Robertson wrote:

Of all sexual conditions complicating insanity, none occupy the importance either in the professional or lay mind that masturbation holds. It is a vice of most frequent occurrence amongst our sane population, and it is almost universally practiced by the insane. That masturbation alone, in the normal individual, produces insanity is certainly not true; for were this the case, the accommodations of our asylums would have to be so increased as to hold at least 500,000 rather than the 5,000 insane credited to our State.

West of the Rockies

Speaker's Corner

A dying patient: shared intimacies and some questions about physician-assisted suicide

The phone rang. I recognized M's voice immediately. She is an intelligent and perceptive woman who played an important role during the electoral campaign in 1994 to legalize physician-assisted suicide (PAS) in Oregon. She had received a telephone call from Jenny, the daughter of an 84-year-old retired engineer, SW, who was dying of lung cancer and desired PAS.

I have been advising many such patients since the Oregon Death with Dignity Act was enacted into law in October 1997. From its inception, I was identified with the campaign to legalize PAS in Oregon, and I make no secret of my belief that PAS may be an acceptable option for some few terminally ill patients who conform with the provisions of the act. The issues raised by a request for PAS are always complex and profound. I wondered what they would be this time.

Jenny had come from her home in British Columbia to a small coastal community in Oregon to help her brother care for their father. Her father had received a course of radiation therapy, but the tumor had progressed. Two weeks before she called, he had had a seizure, after which he was weak on the right side. Many times in her presence he had expressed a desire for PAS. The only doctor in the community had refused his request, advising hospice and home health care. It was difficult to get him to a commode, and Jenny felt that to get him to a doctor's office in a neighboring town would be impossible. SW was dysarthric and his speech was difficult to understand, but he was able to confirm what I had learned from his daughter. He recognized that he was dying, and he wanted an assisted death.

I told him that I would talk with his physician but did not raise his hopes. The physician said that he was sympathetic, but the hospital that employed him had proscribed any involvement in PAS.

A week later I drove down to visit SW. Jenny was out shopping for groceries. SW's son, Peter, greeted me warmly. SW was in bed in the living room of a comfortable townhouse. He was a large man, now somewhat wasted. He had a spastic right hemiparesis, which I thought was probably secondary to cerebral metastases. As I examined SW, his son told me that he had been away from his job for two months caring for his father and that he was concerned his father might be thinking he had become a burden to his children. At this SW exploded, shaking his head violently and exclaiming, "No, no, no!"

I live in Portland, a long distance from the coast. It was not possible for me to perform the duties of the attending physician as mandated by the Oregon Death with Dignity Act. I explained to them both that PAS was unattainable, and that the only option that would allow some control to SW would be for him to resolve to starve to death. It was a somber parting.

Two days later Peter called. His father had decided to starve himself. I advised him to limit fluid only to that necessary to swallow medications and to be sure that hospice personnel knew of the decision, so they would ensure that his father received appropriate palliative care. On several occasions I intended to call but was distracted by other tasks. When I finally contacted Jenny, her father had died.

During subsequent telephone conversations with Jenny and Peter, I gathered details of their father's death and of their reactions during the course of his dying. When SW resolved to starve to death, his mood lightened. For ten days, as he slowly weakened and as his children, with the help of hospice, cared for him, they reminisced about times long past, told stories on themselves, joked, and sang songs half-remembered from their childhood. For Jenny, caring for her father became a blessing, something almost sacred. Peter was more concerned with the day-to-day practicalities.

Then SW had a second seizure, which made swallowing and speech difficult. He struggled to breathe and struggled to die,

desperate for his life to end. That desperation was evident to his children. Peter counted the days, hoping that each would be the last. Jenny was torn. She knew her father needed to die, but caring for him in the most intimate way had taken on a life of its own, and one part of her did not want it to end. After four days they decided that their father needed more intensive relief. Peter wrestled with his belief that morphine doses sufficient to relieve his father's suffering would inevitably shorten his life. As hospice staff were preparing to start an intravenous line, SW died.

For several hours Jenny sat with her father's body. His presence seemed to fill the room. Peter left her alone. He was glad that his father's suffering had ended. Eventually they laid out their father's body. Jenny reluctantly called the funeral home.

Much has been written by physicians about the profound and complex issues surrounding the legalization of PAS. Much less attention has been given to the issues faced by terminally ill patients who desire PAS and their families. SW's death highlights some of their dilemmas and the need for physicians to care better for all dying patients. Why did SW and his children wait so long before actively seeking PAS? Dying patients struggle with many difficult decisions, none harder than whether or not to ask their physician for PAS. The request risks not only refusal but also the unraveling of a relationship with the physician that is crucial in maintaining ongoing care. For SW and his children, a sense of powerlessness inhibited action until his obvious deterioration impelled them to seek further help.

SW died slowly, like most people do in our society, and agonizingly so in the eyes of his children. Yet they had no bitterness, only regret at the manner of his death. Was that because he had had a measure of control over the course of his dying? It seemed to his children that once SW made the decision to starve to death, he was able to bring his life to a satisfactory close by reliving memories that brought him joy.

The children were especially grateful for the help hospice provided. His physician made a timely referral and hospice staff established a relationship that was empathetic. There is much evidence that many referrals to hospice are made very late, shortly before death. For patients who wish to die at home, hospice is an essential element of care and should be involved early.

The patient must affirm that he or she fully understands the import of the request, that he or she expects to die when the medication is taken, and that the request is being made voluntarily. . .

What might have been gained and what might have been lost if SW had been successful in his quest for a physician-assisted death? How would he have decided exactly when to die, and how might he have come to that decision? I have become acutely aware of how some dying patients struggle as they balance the risk of losing the ability to act with their desire to spend another day or two with their loved ones. SW would have died sooner if PAS had been available to him. Opponents of PAS argue that he might have died prematurely, losing an opportunity for the intimacy with loved ones that a good death brings. Would he and Peter and Jenny, who shared so much of themselves, have been deprived of that priceless time? Or would the ability to decide the time of his dying through a lethal dose of medication have facilitated the sharing of such intimacies? Very likely he would have died peacefully. According to information provided by physicians during the first year after enactment of the PAS law,[1] there were no complications in the deaths of the first 15 patients who chose PAS.

Some ethicists have predicted that if SW had received a lethal prescription from his physician, it would have weakened the doctor-patient relationship. Some ethicists have also warned that the general availability of such an option could erode the public's trust in physicians. Yet it could also be argued that the process leading up to the provision of a lethal prescription, as mandated by the Oregon Death with Dignity Act, could have deepened the relationship between SW and his physician. The act stipulates that the patient must make two oral requests for assisted suicide, separated by at least 15 days, and submit a written request signed by two witnesses, one of whom cannot be related to the patient, a beneficiary of the estate, or an employee of a healthcare facility where the patient is receiving care.

In this written request the patient asserts that he or she has been fully informed of the diagnosis, the terminal nature of the disease (which has been confirmed by a consulting physician), the prognosis, the nature of the medication to be prescribed to cause death, the potential risks, the expected result, and the feasible alternatives, including comfort care, hospice care, and pain control. The patient must affirm that he or she fully understands the import of the request, that he or she expects to die when the medication is taken, and that the request is being made voluntarily, with the knowledge that it can be rescinded at any time. The patient must also detail what response he or she has made to the physician's recommendation that family members be informed of the patient's decision to seek PAS. The physician may only write the prescription 48 hours after the patient has submitted the written request and at that time must again confirm that the patient is making an informed decision.

In my discussions with physicians who have been drawn into this process, all have described an emotional intimacy and a profound deepening in the relationships between the patient and his or her loved ones. Most physicians were with their patients when they died. I paid one visit only to SW as he lay dying, but I will not forget him.

Both Jenny and Peter supported their father in his desire for PAS. His death was no less sacred to them, and they shared in it intimately.

Peter A. Goodwin

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COMMENTARY

Debates on physician-assisted suicide are a barrier to real reforms in caring for patients

Life and its end are endlessly fascinating, complicated, and resistant to easy categorization. SW here does not do badly, despite some awkwardness in his care. What is it that Dr. Goodwin would have us learn from the story?

One lesson might be that SW and his family are the prelude to a set of patients who will demand equity and fair access to physician assistance in suicide. Why, after all, does living in a particular community bar one from having this option? If this change happens, it might also presage a gradual course toward ordinariness in physician assistance in suicide. We have few issues that routinely *do* trouble us, that remain troubling over years, and that are valued as persistently difficult. It would be unfortunate and demoralizing to allow the ending of a human life to become routine, even if one believes that the legalization of physician assistance in suicide is good policy. This story as it is told highlights the sacred, mystical, relational, and tender aspects of one life coming to an end. Nothing would be different about the law and public policy, however, if the family were cold-hearted, the patient were whining, the doctor were indifferent, and the course of care were quite mundane. Nevertheless, our intuitions about correctness of policy might well change.

Caregivers have to be careful to attend to the ordinariness of the details of dying, not just the grander poetic aspects. Yet, that very ordinariness is a real threat if good dying comes to include consideration of suicide. Why, after all, is it so important that the physician be involved—might it not in part be the mantra of acceptability granted by "the white coat"?

More important, however, is the terribly persistent fact that most of us do not get such good conditions in which to die. Our dying is much less predictable, our families (if we still have family members capable of giving care) are overwhelmed, our finances are ruined, and our capabilities of self-direction are long since lost. We need to make public policy for these deaths, too. I continue to believe that the most troubling public policy aspect of legalizing physician assistance in suicide is that those who already have so little from the community—the poor, the disabled, the chronically ill—will come to be expected to leave this life willingly when it is convenient for society. It will still be their "choice"—but it might often be the only choice widely accepted by friends and family and might often be the only choice that avoids serious financial and emotional burdens to loved ones. That, it seems, is not a "choice" that warrants the label.

Caregivers have to be careful to attend to the ordinariness of the details of dying, not just the grander poetic aspects. Yet, that very ordinariness is a real threat if good dying comes to include consideration of suicide.

Although it is not particularly germane to the issue of physician-assisted suicide, Dr. Goodwin's essay uses a strange term with regard to the course of deciding to forgo nutrition and hydration: he suggests that the patient "starve to death." The very phrase implies that the patient is feeling great hunger. In fact, most people who are so sick that they will die soon also have very little appetite. Especially with cancer and its attendant weight loss, SW is likely to have been ketotic and dehydrated before making any choice to stop eating and drinking. According to the reports of hundreds of such patients, they experience no hunger and little thirst, so long as the mouth is kept moist. They find it odd to have the day no longer marked by meals—but they do not feel hungry. While they do become more chemically abnormal, that is not a felt experience. Thus, I would never use the term "starve to death."

In sum, SW died pretty much as most people do when they die of a somewhat predictably overwhelming cancer and get good hospice care. They die comfortably. They and their families find the opportunities that they need for closure and meaning. They leave their families with good memories and tolerable bereavement. His time to dying was probably affected very little by his decision to stop eating. His dying might or might not have been different with lethal pills in the closet. Even if he never took them, he might have been tormented by the continual presence of a decision as to what to do.

We are just learning our way as a culture in this new era of having the opportunity to grow old and die slowly. We do not have settled language or categories. We do not know yet what to admire and what to avoid. Certainly all of us mortals need reliably good care, more appropriate financing, and more comprehensive support of families. We need aggressive quality improvement and a commitment to policy reform. Physician-assisted suicide is not the most important issue confronting us. Let us make good care sufficiently comprehensive and reliable so that people no longer fear their care system. Then debates on physician-assisted suicide would be interesting. Now they are both barriers to the real reforms needed and a persistent threat to those whom society sees so often as the unappealing victims of serious chronic illness.

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BOOK REVIEW

Handbook for mortals: guidance for people facing serious illness

by Joanne Lynn and Joan Harrold, Oxford University Press, June 1999, $25.00

One constant over the last half-century has been the growing importance of medicine in American culture. Physicians visiting their patients in the hospital have only to glance at the television screen to see Hollywood's vision of how we should look and act. Nonfictional coverage of medical issues has also increased, with much of human experience and behavior recast in medical terms. The reaction of the medical community to this medicalization of modern society has been complex, but a constant theme has been condescension tinged with annoyance.

What has largely been overlooked in discussions of the popularization of medicine are its benefits. First, there are a growing number of well-written books on medical topics for laypeople. Some of these books could serve as texts for medical students. Examples include How We Die by Sherwin Nuland,[1] Children of Crisis by Robert Coles,[2] False Hopes by Daniel Callahan,[3] The Lost Art of Healing by Bernard Lown,[4] and anything written by Oliver Sacks.[5]

Second, books written for a popular audience broaden the discourse about critical issues. The rapid advances of medical technology, with the attendant rise in expenditures for medical care, have produced a growing number of choices—decisions about costs versus benefits and about unequal access to care. These are not just medical issues; they are societal issues that involve medicine.

Occasionally, an issue directly relating to medicine will arise in which academic medicine takes a back seat, with the most important discussions carried out in the public arena. Examples include the potential uses of micronutrient supplementation and the risks of exposure to silicon and other chemicals. There is no doubt that an appreciation as well for the importance of the emotional, physical, and spiritual needs of the dying person has emerged in large part outside of the medical community, and often in opposition to it. Hospice is based in nursing, not medical, values and flourished in the community long before it was accepted in academic medical centers.

Nan Goldin

Larry and Margot at home, NYC 1995

The target audience for Handbook for Mortals by Joanne Lynn and Joan Harrold is clearly defined; its subtitle is "guidance for people facing serious illness." On the other hand, the subtitle could have been "guidance for people facing serious illness, their families, their friends, their physicians and nurses, and anyone else interested in the fact that we will all die someday." This is a wonderful book, overwhelming in its practicality. It would be of interest to just about everyone.

The 17 chapters are devoted to issues such as living with serious illness; helping family make decisions and give care; getting the help you need; talking with your doctor; controlling pain; planning ahead; forgoing medical treatment; and coping with events near death. Each chapter is subdivided into several sections. For example, the chapter on forgoing medical treatment has sections on stopping treatment; time-limited trials; when food seems like love; the benefits of dehydration at the end of life; choosing to stop eating and drinking; and the many meanings of "do not resuscitate."

Handbook for Mortals is a kind, thoughtful work, full of an appreciation for the heterogeneity of human experience. Why is it that people who work with the dying always sound so much more sensible than the rest of us? There is no cant here. In the first table, "Things to do when time may be short," listed as "very important" are items such as "spend time with people who are important to you," while completing advance directives is in the second group of "important" things. The reflexive action would be to write about the importance of advance directives, which is the medical community's symbol for concern about dying patients.

For most people, death is a tragedy, almost always messy and unpredictable. No amount of planning will eliminate that reality. It is this very reality that is so effectively discussed in Handbook for Mortals. There is no ideology,

just an honest attempt to convey information and give advice. In addition to drawing on their own experience, the two physician-authors employed focus groups with seriously ill people and include considerable input from other professionals in palliative care.

Much of what has been written about serious illness and death comes from a theoretical perspective; even an author as powerful as Elizabeth Kübler-Ross, who came to her ideas through clinical experience, expressed them in theoretical constructs. Her work was groundbreaking, but with the potential to become rigid and codified in the hands of adherents. Thus some hospice workers still obsess about the proper procession of their clients through the various stages of dying.

Such constructs belong in the classroom, not the clinic. Clinical care involves taking care of one individual at a time. In that task, we call upon scientific discoveries and theoretical constructs, but our focus is on the individual patient. It is this spirit of ad hoc practicality that is so wonderfully communicated in Handbook for Mortals. There is no "right way" to be sick or to die. Denial versus acceptance, advance directives versus "keep on keeping on"—there is no right or wrong here, no hierarchy of values for the individual patient to consider. Whatever works is okay. We are not graded on our death. An equally important message is that it is okay to change our minds—for example, to decide to forgo treatment one day and then decide on treatment the next.

Nan Goldin

Larry's table, NYC 1995

Although this book is written to help the individual facing serious illness, it is also a celebration of what it means to be a physician, to slog on through the day-to-day job of helping other people, to continually be open to whatever seems best for each individual. For that reason, the Handbook for Mortals should be a handbook for all health-care workers.

James S. Goodwin

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One hundred years ago

In the Transactions of the Medical Society of the State of California, vol 30, 1900, E.H. Woolsey wrote:

He who eats late suppers, not only directly imposes undue work upon the heart, which must not be always overworked, but imposes, also, extra work upon his liver and other organs of the digestive tract; and they, in turn, reflect back to the heart, through the sympathetic nerves, an excess of physiologic irritation, that finally disturbs the balance of its nervous mechanism, and wears out prematurely its structural elements. And if the late suppers are pickled in the stomach by beer or wine, so as to delay digestion, the liver will give an additional reflex kick to the heart, and both will founder in their functions, and there will ultimately result a vicious circle, expressed by an excess of uric acid in the blood, which will poison the very fountain of life—the sympathetic system; and then will come swift destruction to all functions.

Letter from the South

Circle

Keith Wrenn, Nashville, TN, keith.wrenn@mcmail.vanderbilt.edu

When I first walked into the hospital room, directly off the plane, I was shocked by his unruly white hair, badly in need of a cut by his standards. He smiled at me, waved off my proffered hand, and insisted on a hug, something we rarely did after I was old enough to go to school. His voice was weak.

We also had deeper disagreements about the Vietnam War, Nixon, abortion, and religion. You could say I eventually won most of the battles but, in truth, no one did because they resulted in strained relations.

He had always been able to do about anything. Hale, hearty, and in charge, he took pride in his appearance; regular haircuts whether he needed them or not. He was as strong-willed and opinionated as I.

I grew up in the sixties and we fought the battle of hair. We also had deeper disagreements about the Vietnam War, Nixon, abortion, and religion. You could say I eventually won most of the battles but, in truth, no one did because they resulted in strained relations. Ironically, although my political views were probably more tolerant, I think he had to be immensely more tolerant of me.

Now, while I sit in his room, the hours pass slowly. I doze and wake, try to read a novel, but can't seem to make any real progress. People pass in the hall but they're only a momentary distraction. The nurses come quietly with a smile, in and out as quickly as possible. Too many patients and too little time. The copper-colored bubbles in the tube coming from his nose are mesmerizing. Sometimes they resemble a coiled spring when the light is just right. Other times, as the light fades, the bubbles take on the appearance of a snake skin.

He sleeps a lot and I watch him, his chest rising and falling with some effort. The laxity of his lower jaw makes it seem as if it has shrunk in relation to his upper jaw. He mumbles about things in the past, some of which I understand, most of which I don't. Often he awakes confused, calling for my mother or asking me about something I cannot answer. Sometimes in the space of minutes, he will be in several different places.

He's tethered by the IV line coming from his chest to a bedside pole. One of the three pumps on that pole seems always to be beeping. I can't do anything about these malfunctions, and I have to push the button for a nurse. The bag that drains the colostomy in the middle of his abdomen has to be emptied fairly frequently. He coughs a lot and has to spit into one of those kidney-shaped yellow basins, always just out of reach on the bedside table. Most of the sputum clings to his chin and it's up to me to wipe it off and dispose of it. We work together on positioning the plastic urinal between his legs. These acts punctuate the hours.

The same old resentments have been resonating at the back of my mind, a mixture of guilt and irritation. I always feel like a teenager when I come "home," and this time I left my own family, my job, and a million deadlines.

This morning he asked me to help him up. He wanted to clean himself at the sink, a first during my visit. After shakily arising from the bed, the hospital gown flapping open in the back, he wobbled to the sink. With me at his elbow he took out his personal kit, and as he opened it, a host of familiar smells assailed me: aftershave, deodorant, and hair tonic. I remember, as a small child, I would stand and watch him in the early morning as he prepared to go to work. All I wanted was to be like him.

With me at his elbow he took out his personal kit, and as he opened it, a host of familiar smells assailed me: aftershave, deodorant, and hair tonic. I remember, as a small child, I would stand and watch him in the early morning as he prepared to go to work. All I wanted was to be like him.

I watch him now lather his face and start to shave, still such a familiar thing, and I am overcome by the melting away of my resentment. It almost brings me to tears, years of unspoken and unresolved hurt dissolving. How can the act of dying have such a profoundly healing effect?

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All courses and meetings listed are approved for Cat 1 credit toward the CMA Certificate in CME. To list accredited courses here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

JANUARY 21-23, 2000: **The 38th Clinical Conference in Pediatric Anesthesiology.** The Pediatric Anesthesiology Foundation and Children's Hospital Los Angeles at Disneyland Hotel Anaheim, CA. 13 hrs Cat 1. Contact David J. Steward, (323) 669-2262; Fax (323) 660-8983.

CARDIOLOGY

DECEMBER 17-19, 1999: **The 16th Advances in Heart Disease.** The Grand Hyatt, San Francisco on Union Square, San Francisco, CA. 16 hrs Cat 1. $490-565. Contact American College of Cardiology, Registration Secretary, (800) 253-4636, ext. 695; Fax (301) 897-9745.

JANUARY 13-16, 2000: **NewEra Cardiac Care 2000: Leading-edge, Minimally Invasive Cardiac Therapies.** Coronado Island Marriott Resort, San Diego, CA. Contact Karen Morgan, (760) 751-8841; Fax (760) 751-8842; karen@amainc.com.

JANUARY 17-21, 2000: **Cardiovascular Conference at Snowmass.** American College of Cardiology at Snowmass Conference Center, Snowmass, CO. 23 hrs Cat 1. Contact American College of Cardiology, Registration Secretary, (800) 253-4636, ext. 695; Fax (301) 897-9745.

JANUARY 21-23, 2000: **Clinical Nuclear Cardiology: Case Review with the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles, CA. 20 hrs Cat 1. Contact American College of Cardiology, Registration Secretary, (800) 253-4636, ext. 695; Fax (301) 897-9745.

FAMILY PRACTICE/PRIMARY CARE

NOVEMBER 18-20, 1999: **Women's Health Issues in Primary Care.** UCSD at La Jolla Marriott, La Jolla, CA. 15 hrs. $350. Contact UCSD, (858) 534-3940.

DECEMBER 2-3, 1999: **Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco, CA. 13 hrs Cat 1. $370. Contact UCSF Department of Medicine, CME, (415) 476-5208.

DECEMBER 10-12, 1999: **Issues in Women's Health.** Medical Education Resources at Tropicana Hotel, Las Vegas, NV. 11 hrs Cat 1. Contact Linda Main, (800) 421-3756, Fax (303)798-5731.

INFECTIOUS DISEASES

DECEMBER 1, 1999: **AIDS-Associated Malignancies.** UCSF at Sheraton Palace Hotel, San Francisco, CA. 7 hrs Cat 1. $195. Contact UCSF Department of Medicine, CME., (415) 476-5208.

DECEMBER 2-4, 1999: **Comprehensive Review of HIV Management–Winter.** UCSF at Sheraton Palace Hotel, San Francisco, CA. 24 hrs Cat 1. $455. Contact UCSF Department of Medicine, CME., (415) 476-5208.

OB/GYN

DECEMBER 10-12, 1999: **Issues in Women's Health.** Tropicana, Las Vegas, NV. CME 11 hrs Cat 1. Contact Linda Main, (800) 421-3756; Fax (303)798-5731.

ONCOLOGY

DECEMBER 5, 1999: **California Tumor Tissue Registry 107th Semi-Annual Cancer Seminar: Surgical Pathology of Tumors: What Have We Learned In This Century?** CTTR at Ritz-Carlton Hotel, San Francisco, CA. 10 hrs Cat 1. Contact CTTR, c/o Loma Linda University School of Medicine, (909) 558-4788; Fax (909) 558-0188; cttr@linline.com.

PEDIATRICS

NOVEMBER 13-14, 1999: **Pediatrics for the New Millennium: A National Seminar.** College of Physicians and Surgeons of Columbia University at New York Marriott Marquis, New York, NY. Contact Center for Continuing Education, (212) 781-5990; Fax (212) 781-6047; cme@columbia.edu.

GENERAL

NOVEMBER 12-15, 1999: **Conversations in Spanish.** Maricopa Integrated Health System at Glendale Adventist Medical Center; DECEMBER 3-6, 1999: San Francisco, JANUARY 21-24, 2000: Scripps Hospitals, San Diego; 36 hrs $695. Contact Rios Associates (520) 907-3318 or (619) 218-4875; Fax (520) 325-4258.

JANUARY 13-15, 2000: **Health-Care Systems: Ethical and Economic Considerations.** UC Davis Health System, UC Davis School of Medicine Alumni Association at Sacramento Hilton Inn, Sacramento, CA. 12 hrs Cat 1. Contact Vickie Hidalgo, (916) 734-5774; Fax (916) 734-8966, vickie.hidalgo@ucdmc.ucdavis.edu.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact CMA, P.O. Box 7690, San Francisco 94120-7690. (800) 882-1262.

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State Associations should send their CME listings for publication to:

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WJM Western Journal of Medicine,
PO Box 7690, San Francisco, CA 94120-7690;
tel 415-974-5977; fax 415-882-3379;
wjmsf@pacbell.net.

Breast Cancer, Early Detection and Control. Texas Medical Association. CD ROM. $70. 2 hrs Contact Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

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To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850. Brochures, course information, and registration forms are available from the contact person or organization.

TUESDAY NOON CONFERENCES—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact Jean A. Kline, (303) 425-2951.

FIRST WEDNESDAY OF EACH MONTH—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact Colorado Society of Neurologists, (303) 449-3566.

SECOND WEDNESDAY OF EACH MONTH—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo: Contact University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; Fax (303) 372-9065.

IDAHO

To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930. Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.
NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

EVERY FIRST AND THIRD TUESDAY: **Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact Thomas A. Naegele, DO, (505) 275-7267.

DECEMBER 2-3, 1999: **Primary Care Orthopaedics.** Hoffmantown Conference Center, Albuquerque, NM. Contact UNM Continuing Medical Education, (505) 272-3942.

DECEMBER 3-4, 1999: **Trauma Update.** Hilton Hotel, Albuquerque, NM. Contact UNM Continuing Medical Education, (505) 272-3942.

JANUARY 13-16, 2000: **Advanced Life Support in Obstetrics.** UNM Continuing Education Conference Center, Albuquerque, NM. Contact UNM Continuing Medical Education, (505) 272-3942.

JANUARY 21-22, 2000: **30th Annual Winter Pediatric Orthopaedic Seminar.** UNM Continuing Education Conference Center, Albuquerque, NM. Contact UNM Continuing Medical Education, (505) 272-3942.

SATELLITE COURSES

Contact Joe Treat or Jim Cato, Immunization Program, (505) 827-2366.

UTAH

All courses listed meet the criteria for Cat 1 of the Physician's Recognition Award of the AMA. To list AMA Cat 1 CME courses, send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address. NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

WEEKLY: **Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact UUSM.

WEEKLY: **Pediatric Grand Rounds.** Contact PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Cat 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA98121; or phone (206) 441-9762 or (800) 552-0612.
Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME Harborview: Contact Gayle Splater, (206) 223-5953. **PCMS CME:** Contact Executive Director, College of Medical Education, (206) 627-7137. **U/W (University of Washington):** Contact U/W School of Medicine, (206) 543-1050. **VMMC (Virginia Mason Medical Center):** Contact Linda Orgel, (206) 340-2058. **WSMA:** Washington State Medical Association, Continuing Medical Education, (206) 441-9762.

WYOMING

All courses meet the criteria for Cat 1 of the Physician's Recognition Award of the AMA. To list AMA Category 1 CME courses here, send information at least two months in advance to the Medical Education Committee, Wyoming Medical Society, P.O. B ox 4009, Cheyenne, WY 82009; email skeefe@wyomed.org; phone 307 634-2424; Fax 307 632-1973.

The secular West

David Heiden

Coptic Christian services held by refugees from Tigre Province of Ethiopia at Fau 3 refugee camp, Sudan 1985.

These images of prayer have remained with me: a Coptic Church service; a Koran school where 11 young boys sat in a circle around a bonfire, holding 4-foot-long wooden boards with a verse written in soot-ink and chanting together as darkness fell; a Hindu Kumba Mela festival where 15 million Indians attempted to bathe in the Ganges at the same place and on the same auspicious day; Tibetan pilgrims walking inside the dark Johkang monastery in Lhasa, past rows of sour-smelling yak butter candles. Each time I could sense a broadly shared passion and a trust in something beyond the material and the rational. I learned that I lived in the "secular West" by seeing the opposite.

In a secular culture, it is harder to confront issues that are fundamentally not rational or material. Doctors have special technical expertise, but it is partly by default that we get asked about issues that have a spiritual dimension—like euthanasia, suicide, or abortion.

David Heiden is an ophthalmologist practicing in San Francisco.

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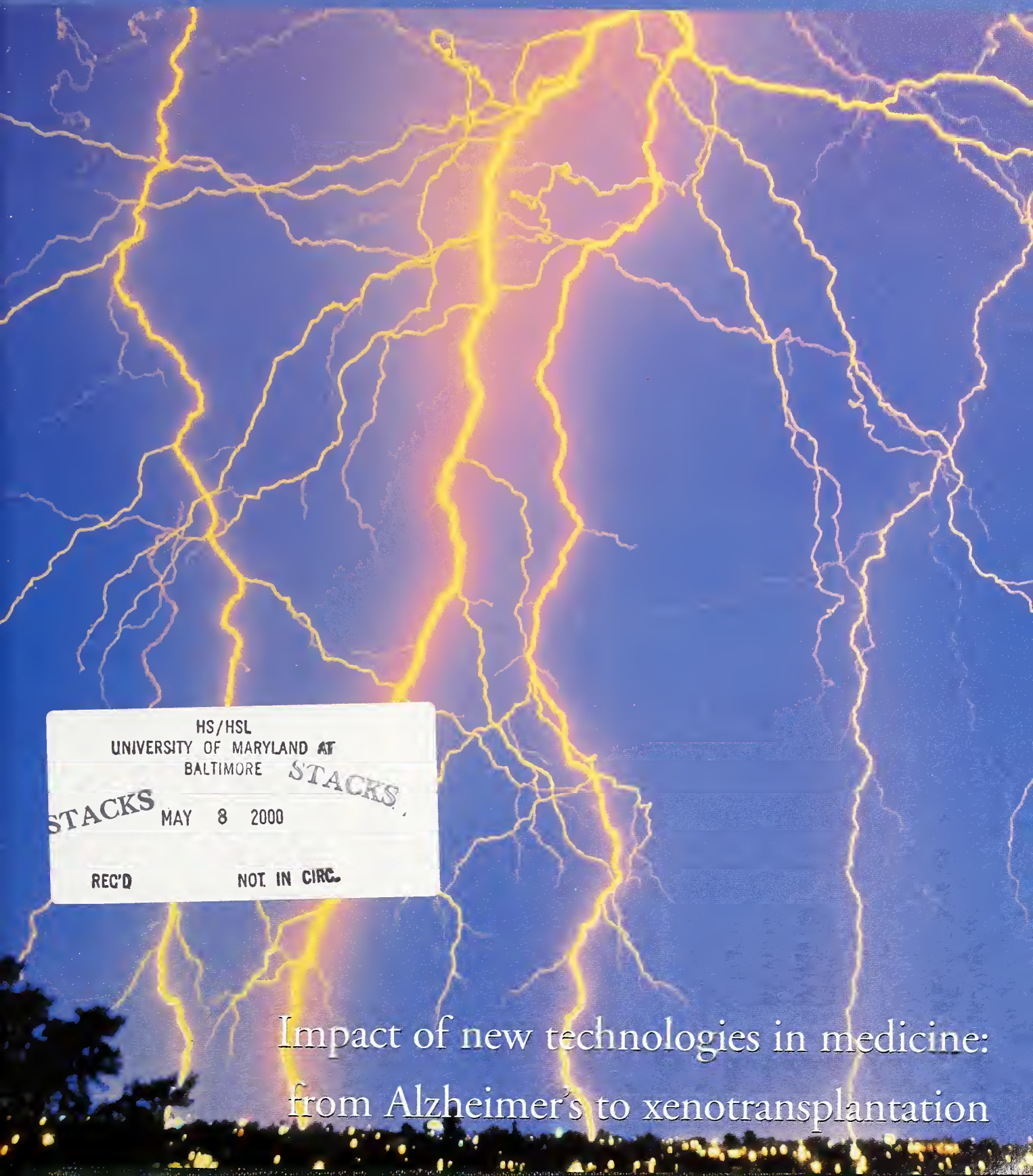

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Impact of new technologies in medicine: from Alzheimer's to xenotransplantation

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Editor's Pick

Japanese engineers have designed a toilet that analyzes urine for glucose concentrations, while scientists at John Hopkins Institute have developed a biochip photosensor which will be used as a retina for patients with macular degeneration. The brave new world of medical technologies is already upon us and with it the opportunity to offer patients diagnostic and therapeutic advances that just a few years ago were the material of science fiction movies.

In this issue, wjm is joining other medical journals worldwide in looking at the impact of new technologies in medicine, not only in terms of new gadgets but in a wider ethical context. Most of these new technologies will be less invasive and more personally tailored to individual patients. Many will be costly and only available to the developed world. What we must ensure is that all are fully evaluated before being integrated into health care and that the ethics of using them are explored and discussed not just by physicians but by everyone.

Some of the new technologies that are in place are already causing controversy. On p 293, Gary Small suggests that positron emission tomography (PET) can offer an earlier diagnosis of dementia—a disease that is currently diagnosed on the basis of clinical findings. The theoretical advantage of early diagnosis is that patients could be treated with the new drugs that some claim are said to improve cognition and perhaps delay placement in a nursing home. Not so, says Kenneth Brummel-Smith, on p 294 there is no evidence that earlier diagnosis is associated with improved quality of life or cost savings. Will this evidence deter anyone from using this new diagnostic tool? Probably not, but we need to insist that proper outcome measures and appropriate cost-benefit analyses must be part of the assessment of any new technology. Similarly on p 338, Allen J Taylor argues that electron beam computed tomography accurately quantifies the extent of coronary calcification and is an important screening tool with the benefit that is useful because patients with positive scans can be offered aggressive risk factor modification and preventive treatments. Jerry Hoffman's commentary (p 341) warns that when new technologies undergo real testing "—not measuring some parameter, or imaging some vessels, but seeing if they improve outcome—many prove far less beneficial, and are associated with adverse consequences." These adverse consequences can include unnecessary worry and the medicalization of healthy people.

While technology will clearly offer us many new tools, the advantages of technology can be overstated. On p 322, Charlie Wilson warns that sensors such as an electronic "nose" that can detect the odors of growing bacteria, will not transform medicine overnight. Within the next 10 years, however, he expects these devices that can detect physical biological and chemical signals and provide a way for them to be measured and recorded, to change the way hospitals operate. Sensors in beds will detect vital signs and abnormal blood chemistries, making the central laboratory largely redundant. Technologies involving gene chip arrays can determine variations in DNA sequences for individual patients, so they can be offered tailored drug regimes that suit their genome. On p 328, Wolfgang Sadée explains that variation in response to cancer chemotherapy may be explained by genetic variability. A dramatic example is tioguanine, which can kill patients who are genetically unable to inactivate the drug. To detect susceptible patients genotyping for the gene encoding thiopurine methyltransferase is already standard practice at the Mayo Clinic in Rochester and other major cancer centers.

The opportunities that new technologies offer also lead to provide bring ethical considerations. New technologies may be able to offer genetic engineering, which Caplan argues (p 335) despite connotations of Nazi Germany may be palatable on an individual basis.

The developing world of course does not have the luxury of dappling in eugenics or being able to afford designer drugs. But technology will not pass them by. Vaccines, says Margaret A. Liu, have transformed the planet, eliminating smallpox and offering hope for the future in such diverse areas as cancer gene therapy, hypercholesterolemia and diabetes. Yet these tools will come at a real cost, forcing governments and organizations to make painful decisions. The developers and manufacturers will need to place profit in an appropriate context along side human need and suffering. Vaccines against HIV are much more likely to be affordable to the developing world than combination drug therapies. On p 363, James Kahn explains how an effective HIV vaccine has been built, while Leslie E Wolf and Bernard Lo (p 365) discuss the ethics of HIV vaccine trials.

New technologies underline the problem of educating future physicians. A teaching approach of how to learn rather than what to learn may be more realistic. On p 325 Allen Shaugnessy and David Slawson argue that we need to pay attention to how information is delivered to physicians and how they can be taught to assess both its relevance and quality.

Yet after all the scans and probes and chips, the physician will still be left to care for the patient who is scared, confused and vulnerable. It is here where technology will have the least impact, for it is here where the art of medicine will not be replaced by science of medicine. To remind us that it is still the person, rather than the blood level, organ disease or tumor mass that needs treating, a patient, movingly describes what it's like to be diagnosed with dementia. The magnetic resonance imaging test and other diagnostic tools confirm that she has Alzheimer's disease yet she has started a new job and has a full and happy life. Her words, "I must not let labels or tests determine my identity" are a reminder to us all.

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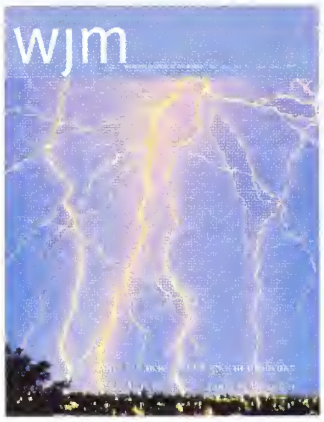

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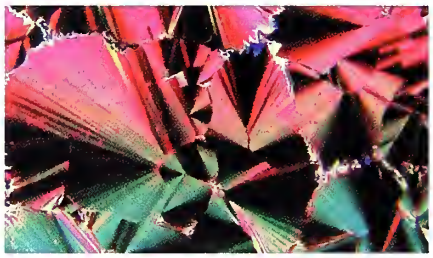

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Op/Ed

Positron emission tomography scanning for the early diagnosis of dementia

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Would improve quality of care for patients and save money

Dementia affects about 8% of people age 65 years and older.[1] About 4 million people in the US have Alzheimer's disease, the most common form of dementia in later life. The annual cost of this disease, including medical, home care, and taking into account the loss of productivity among caregivers, is estimated to approach $90 billion.[2] Although Medicare, Medical, and private insurance cover some direct costs, families assume the greatest expense.

Recognition of dementia is particularly difficult in its early stages when family members and physicians often incorrectly attribute the patient's symptoms to normal aging.[3] Systematic studies indicate that the frequency of unrecognized memory impairment, beyond that associated with normal aging, or dementia diagnosis can range from 50% to 90% of patients.[4] Thus, in some settings, physicians identify only 1 out of 10 people with dementia.

Neuroimaging studies are not used routinely to assist in diagnosis and differential diagnosis of dementia. Usually, clinicians obtain computed tomography or magnetic resonance imaging scans. Such structural neuroimaging studies are typically normal in-patients with organic dementias and have only limited usefulness, often providing nonspecific information about cerebral atrophy and rarely uncovering treatable lesions. In fact, the overinterpretation of structural imaging studies may contribute to overdiagnosis of vascular dementia.[1] By contrast, functional imaging – particularly positron emission tomography because of the biologic information it provides – can lead to a positive diagnosis of early Alzheimer's disease. In a study of patients with dementia who were followed clinically for at least 3 years, we found that baseline positron emission tomography scans showed greater diagnostic sensitivity and specificity than conventional clinical assessment.[5] With a prognostic sensitivity of greater than 90%, positron emission tomography was found to provide a diagnosis 2 to 3 years before manifestation of dementia-related symptoms.[5] Previous studies had also shown that the characteristic parietal/temporal lobe pattern of metabolic dysfunction observed on a positron emission tomography scan can be recognized months and sometimes years prior to clinical confirmation of Alzheimer's disease.[6]

Clearly, many patients with Alzheimer's disease are not recognized and fail to receive treatment, particularly early in the disease course when intervention is most effective.[1] Because of the loss of central cholinergic neurons that occurs in association with Alzheimer's disease, drug development has focused on improving cholinergic function. The U.S. Food and Drug Administration has already approved two drugs that improve cholinergic function, tacrine and donepezil. Multisite, placebo-controlled trials have shown that such cholinesterase inhibitors improve or delay decline in memory and other cognitive functions in patients with mild to moderate Alzheimer's disease.[1] Other therapies have shown efficacy. Vitamin E has been shown to delay functional decline[7] and antidepressant and antipsychotic medications to improve behavioral complications.[1]

Positron emission tomography is approved by the Food and Drug Administration and is reimbursed for many indications by private insurance providers, but the Health Care Financing Administration reimburses for only epilepsy, cardiovascular disease, melanoma, lymphoma, and lung and colorectal cancers. Although the Health Care Financing Administration is considering broad reimbursement policies for positron emission tomography, Medicare does not currently fund these scans for the differential diagnosis of dementia. But are we saving money by avoiding a procedure that improves early diagnostic accuracy? If, indeed, positron emission tomography increases diagnostic accuracy, particularly early in the disease course, how might these factors influence health care costs?

Patients would probably be treated earlier, with improved daily functioning and quality of life. Cholinesterase inhibitor treatment also delays nursing home placement.[8,9] In one study, the rate of nursing home placement in patients not receiving donepezil over a 6-month period was twice as high as that for patients receiving this drug.[9] In addition, non-pharmacologic interventions, such as caregiver education and emotional support, also delay nursing home placement.[10] Other economic studies indicate that use of donepezil by patients with mild to moderate Alzheimer's disease is associated with lower 5-year costs and slower progression to advanced stages when compared with usual care with no donepezil.[10] When uncertain about diagnosis, clinicians often perform costly repetitive examinations. The greater accuracy of positron emission tomography can facilitate early intervention. Offsetting the costs of anti-dementia medications would be the cost savings from delayed placement in nursing homes and the avoidance of repetitive examinations.

For a comprehensive analysis of health care costs, the economic outcomes of different approaches must be considered. In such an analysis, the costs of delay in diagnosis,

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The views expressed are those of the author and do not necessarily represent those of the Department of Veterans Affairs

patient and family preferences for second opinions, unpaid caregiver costs, or additional days in nursing homes also must be evaluated. An initial clinical assessment that includes a positron emission tomography scan (approximately $1200 for a brain scan) could save unnecessary repetitive tests (ranging from $500 to $2000 each) and delay in nursing home placement (about $40,000 per year).

Definitive diagnosis and treatment early in the course of the disease would likely decrease both direct and indirect costs. The improved diagnostic accuracy that positron emission tomography scanning provides argues for including such scans as part of the evaluation of dementia, particularly in patients with mild cognitive impairments.

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Positron emission tomography for the early diagnosis of dementia

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What's the primary care provider to do to diagnose and treat Alzheimer's disease?

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As the baby boomers enter the geriatric age group, the prevalence of dementia will rise dramatically and the cost of their care will be staggering. In the past decade, new drug treatments have garnered the attention of clinicians, family caregivers, and patients alike. Yet many primary care providers, and payers, remain skeptical about their benefits.

Dementia is one of the most stressful conditions that primary care providers must manage. Physicians are not likely to notice cognitive decline during a brief office visit without using cognitive screening tests. Physicians often view the assessment and treatment of dementia as time consuming, poorly reimbursed, and unlikely to much benefit the patient. As a result, dementia is often not diagnosed and physicians are reluctant to use standardized assessment tools. When dementia is diagnosed, physicians concentrate on the immediate medical concerns and neglect issues of long-term care and the needs of families and caregivers. Satisfaction with dementia care is often low; in one study, only 18% of caregivers thought they were given enough information about the disease.[1]

Guidelines for diagnosis of dementia recommend that neuroimaging should be considered when certain clinical features are present, such as localizing findings, or atypical presentations.[2,3] Similarly, the traditional extensive laboratory work-up has been questioned given that it is unlikely that conditions such as B_{12} deficiency or syphilis will be found in primary care settings.[4] A committee of the National Chronic Care Consortium and Alzheimer's Association has proposed a standardized set of screening and diagnostic studies that are most appropriate in managed care.[5] Even with these guidelines, however, dementia is currently a diagnosis made on the basis of clinical findings.

The lack of a diagnostic test has led Dr Small to recommend the use of positive emission tomography (PET) to allow for earlier diagnosis.[6] This recommendation is premature. First, no evidence exists that earlier diagnosis is associated with improved quality of life or cost savings. Second, while cholinesterase inhibitors show promise in the research setting, this promise has yet to be realized in actual practice.

The goal of early detection of disease is to provide

interventions that lead to demonstrable changes in the natural history of untreated illness. There is no such evidence available in Alzheimer's disease. The randomized trials of tacrine (Cognex) and donepezil (Aricept) enrolled subjects who would generally be considered to have moderate, not early, dementia. For instance, the mean Mini Mental Status score of participants in the tacrine trials was 16 to 19 out of 30, a score indicating moderate impairment.[7] Although donepezil trials have included some patients with higher scores, most are in the 18 to 21 range[8]; there are no published long-term studies with patients having scores exclusively in the 21 to 26 range. These studies also have excluded all patients with comorbid conditions. Even if positron emission tomographic scanning can be shown to reliably detect those with Alzheimer's before the onset of clinical symptoms, treatment studies would be needed to demonstrate such early detection is beneficial.

To be judged beneficial, early treatment would need to show improvements in cognition, physical function, behavioral problems, or cost savings. Unfortunately, in many cases the "improvements" in cognition in trials of cholinesterase inhibitors were not detectable to families or clinicians.[9] It is doubtful that early diagnosis with positron emission tomographic scanning would allow treatment to improve physical function (eg, Activities of Daily Living) because these functions are not affected in the early phases of the disease. A decline in functional ability, not cognition, is what stresses families most and leads to placement in nursing homes. No randomized, placebo-controlled trials of cholinesterase inhibitors have shown a reduction in nursing home placement. Vitamin E has been shown in one randomized trial to reduce nursing home utilization and maintain function, but this study also involved subjects with more advanced dementia so it does not answer the question whether early treatment will reduce long-term costs.[10]

Finally, there is an ethical dilemma to early diagnosis of dementia. Diagnosis "2 to 3 years before manifestation of dementia-related symptoms" would only be acceptable if treatment at that stage led to marked improvements in outcomes. Without such hope for treatment early diagnosis would be cruel. Consider the psychological impact on the patient, a person's employment or insurance coverage, or the effect on the family if we were to diagnose dementia before we were able to make a meaningful difference in their lives through treatment.

Prospective, controlled trials in representative populations (ie, those in primary care settings who have typical comorbid conditions) are needed. Such trials must measure meaningful outcomes such as caregiver burden, costs, and functional changes that are appreciated by untrained family members. When evidence exists that early diagnosis and treatment is beneficial, then positron emission tomography and treatments such as cholinesterase inhibitors can be considered the standard of care and worthy of insurance coverage. In the meantime, we should redouble our efforts to educate family members in the recognition of cognitive changes, primary care physicians how best to diagnose and manage dementia, and advocate to managed care plans and other forms of insurance payers to adequately fund management of this devastating disease.

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Correction

We regret the omission of Ronald M Davis and Edward H Wagner as co-authors of the call for papers addressing chronic disease management in the June issue of wjm.

The politics and prevention of gun violence

Physicians are morally obligated to help prevent gun trauma

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For years, gun violence has been a major public health concern in which physicians and other healthcare providers have played important roles. Only recently, however, after mass shootings in Colorado, Georgia, and Los Angeles, has the prevention of gun violence become a priority for policymakers. Preventing gun violence requires the use of a variety of strategies including lawsuits. But the gun industry, and the politicians who protect it, have launched a nationwide campaign to block the lawsuits that could promote prevention. Physicians and other healthcare providers concerned with preventing gun violence must help defeat this campaign.

Although violence generally has declined in recent years, guns remain a leading cause of morbidity and mortality in the United States. In 1997, over 32,000 people were killed by guns: about 89 people every day.[1] A large proportion of these deaths, over 17,500, were suicides.[1] The rate of homicides exceeds that of suicides in urban areas but suicides are more common in rural communities.[2] An average of 12 young people (from infancy to age 19 years) die from gunshot wounds every day in America, at least one of whom is killed accidentally.[3] For every homicide caused by guns, there are at least three, and perhaps as many as seven, nonfatal injuries.[4] Although some people buy guns to protect themselves at home, household firearms are most likely to be used against a family member or someone else known to the gun owner.[5] Indeed, having guns in the home increases the likelihood of homicide nearly threefold [6] and increases the likelihood of suicide fivefold[7] These statistics show the high risks associated with gun ownership and the adverse public health consequences of gun violence. They also suggest that the problem is complex. Homicides, suicides and unintentional shootings each have unique characteristics, and the nature of gun violence varies widely across geographic, demographic and socioeconomic boundaries. This complexity poses challenges for prevention, highlighting the need for a multipronged approach.

Recent events in Congress have shown that there is strong opposition to the enactment of legislation designed to reduce injuries from guns. A modest proposal to require that background checks be run on those who buy guns at gun shows failed, despite having strong public support, largely because of the political influence of the gun industry and its advocates.[8] Thus, many sales at gun shows occur outside any regulatory system, which allows guns to be sold without any accountability to criminals, children and others who are legally prohibited from purchasing guns. This, and other legislative loopholes, hinders public health efforts to reduce access to guns by people who should not have them.

Other weaknesses in the regulatory system further hamper prevention. Unlike the situation for every other product sold in America, neither the Consumer Product Safety Commission[9] nor any other agency[10] has the authority to require that changes to the design of guns be made or that product recalls be ordered. The Bureau of Alcohol, Tobacco and Firearms, in the Treasury Department, oversees some aspects of distribution but its regulatory power is narrow and its funding limited. The Department of Justice sets standards for guns used by law enforcement agencies but it cannot apply those standards to guns sold to civilians. The Federal Trade Commission has never challenged advertising claims made by the gun industry about the purported benefits of gun ownership, despite public health research that clearly shows the falsity of those claims.[11] The gun industry and its well-organized advocates work vigorously, and often successfully, to preserve this weak oversight.

When the standard tools of prevention, legislation and regulation fail, as they have for gun trauma, those seeking to prevent such injuries reluctantly turn to litigation.[12] Successful litigation, though a crude device, creates indirect incentives for change by shifting the costs of risky behavior or products from the consumer to the industry that produces the risk.[12] The threat of large awards for damages can motivate product manufacturers to redesign their products and modify their promotional and distribution practices. Litigation has forced manufacturers to make safety improvements in products ranging from cars to hot water vaporizers to explosives.[13] These changes are public health interventions because they control the product as a vector, potentially reducing the likelihood or the severity of injuries caused by the product.[15]

Lawsuits against the gun industry, filed by private individuals and over 20 municipalities, seek to prevent injuries by shifting some of the costs of the trauma associated with guns back to the industry. If these lawsuits are successful, the gun industry will incur costs that should motivate it to design, market and distribute guns in a manner that reduces injuries. In the context of a public health problem that has been inadequately addressed by legislation and regulation, these lawsuits are a public health strategy of last resort.

In response, the gun industry has proposed legislation, in many states and in Congress, that would bar these lawsuits. The industry has already helped pass these laws in at least 13 states including Nevada, Arizona, and Georgia. These laws will eliminate an important public health strategy for preventing gun injuries and set a dangerous precedent that other industries that produce harmful products will surely seek to repeat. Physicians and others dedicated to preventing gun injuries should oppose this legislation to protect current and future public health efforts. In addition to opposing barriers to prevention strategies, physicians should also discuss the health risks of firearm ownership with their patients[14] and work for laws to prevent the injuries and death associated with guns. As in the case of tobacco, these advocacy efforts can help us set a new agenda that emphasizes prevention over profits. Public health litigation is an important component of that effort. Given the impact of gun violence on health, physicians are morally obligated to help prevent these injuries. Physicians and other health care providers who want more information can contact the Bell Campaign (1-800 - RINGING) or visit their website http://www.bellcampaign.org which has a searchable database on gun trauma prevention websites. Two other excellent resources include: The Johns Hopkins Center for Gun Policy and Research (http://infosys.jhsph.edu/centers/gunpolicy/) and the Violence Policy Center (http://www.vpc.org/).

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Physicians' unions must be able to strike

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It may be the best way to protect patient's care

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The number of doctors who are unhappy with the quality of their professional lives is growing alarmingly. Doctors are expressing fury and frustration over a managed care system that erodes their autonomy and allows Health Maintenance Organizations to base decisions on saving money instead of saving lives. If doctors do not speak out for their patients' well being, no one will. At the same time, many doctors feel managed care makes it impossible to fulfill their role as patient advocates. In response to this dissatisfaction, the American Medical Association has set up a "collective bargaining unit." While many physicians are turning to doctors' unions to find support for both themselves and their patients, the American Medical Association House of Delegates believes it has an alternative.

Although the House of Delegates voted to form a labor organization, it carefully avoided calling it a "union" and was quick to emphasize the difference. In contrast to traditional unions, the American Medical Association has a no strike policy. President elect Randolph D. Smoak Jr, has clearly stated, "We would never invoke a strike,"[1] pointing to violations of ethics and of the Hippocratic oath."[2] Yet strikes are the ultimate collective bargaining tool. If those with whom you are bargaining know you would never invoke a strike, you deal from a position of weakness. In the opinion of Robert L. Weinmann, president of the Union of American Physicians and Dentist president, "If you've given away your best weapon, you're like a general who says in advance he won't use ground troops."[3]

A "never-strike" collective bargaining unit is not the only mixed message the American Medical Association is sending. Their Board of Trustees does not want a labor organization,[4] their House of Delegates does,[4] and neither seems to understand that the ability to strike is a necessary part of having an effective union. Meanwhile, physicians in private practice are excluded from many of the benefits of organized labor. Federal law currently prohibits health care professionals in private practice from collectively bar-

gaining; however, legislation supported by doctors' unions and the American Medical Association could change this (H.R. 1304, The Quality Health-Care Coalition Act).

Independent surveys show that 80% of customers believe insurance plans often compromise the quality of care to save money.[5] The New England Journal of Medicine mentioned "restrictions on their personal time, financial incentives that strain their professional principles, and loss of control over their clinical decisions "[6]as a few of the frustrations doctors face. Physicians in private practice must collectively bargain to regain the rights they have lost, and prevent further erosion of their autonomy. Denying this relief portends the demise of private practice. The failure of the United States Congress to pass a legitimate Patients' Bill of Rights makes this all the more critical.

Physicians in private practice often feel as if they were going to work in a straight jacket. The insurers and regulating bodies place such onerous restraints on them that they are becoming virtually locked out. The concept of a "lock out" is one that the American Medical Association and many others fail to understand. When health care providers' salaries dwindle, their malpractice and medical licenses are placed in jeopardy, their best medical knowledge is ignored, and they must deal with Health Maintenance Organizations that act with impunity, they are virtually "locked out of practice." When this escalates to the point that care can no longer be provided, physicians must be permitted to close their doors. Some would mistakenly call that a strike.

Unions offer doctors a chance to recapture their profession, to turn the voice of one into the voice of many. For the private practitioner, unions offer a wide array of benefits. They can help to negotiate individual Independent Physician Association/Health Maintenance Organization contracts and improve working conditions, assist in getting claims paid by third party payors who routinely lose, delay, or deny these payments. They can aid in developing public relations campaigns to educate the public and expose the problems of managed care. Unions can provide private practitioners with access to sympathetic legislators. Doctors unions such as the Union of American Physicians and Dentists provide these benefits and more to their members.

Hippocrates could never have imagined the adversity managed care could cause, yet he would surely have wanted physicians to do everything in their power to continue treating the sick even if that meant joining doctors unions. Letting those who look at the bottom line and not at patients to dictate how we practice medicine violates our oath. Doing what is necessary to assure that we are able to provide quality care for our patients does not.

Chief executive officers of health care organizations earn millions of dollars by depriving patients of care. Advocates for managed care employ scare tactics threatening the loss of health care benefits if we dare to give patients rights or allow private practice doctors to collectively bargain. Unions could decrease the cost of health care by directing money into patient care instead of the chief executive officers' pockets. Unionizing is the best way to protect our patients and preserve our role as healers.

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Physicians for Responsible Negotiations will be heard

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Patients do not want their doctors to strike

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Physicians for Responsible Negotiation was formed last June after the American Medical Association House of Delegates last June requested the formation of a national labor organization that was unaffiliated with organized labor. The organization was to be committed to the ethical principles of the American Medical Association Council of Ethical and Judicial Affairs. The preamble to Physicians for Responsible Negotiation's constitution clearly states that the organization will not strike. Withholding needed patient care is never appropriate. Besides, labor experts claim that strikes alienate the public and are ineffective, especially in healthcare.

Despite its decision not to strike, Physicians for Responsible Negotiation will be heard. Physicians will be able to use numerous other strategies to grab the attention of managed care plans and other employers who insist on

policies and practices that compromise physicians' ability to practice good medicine. For starters, as soon as Physicians for Responsible Negotiation is recognized by the National Labor Relations Board, employers will have to sit down at the table with physicians to discuss their concerns in good faith.

In addition, Physicians for Responsible Negotiation will enable physicians to join together to mount informational campaigns that can educate patients, the media and lawmakers about employer plans and practices that do not allow for good patient care. Informational pickets are just one vehicle that could be used.

It is important to emphasize that, legally, negotiations are only protected between employee physicians and employers, but not for self-employed physicians in their dealing with payers. The exception is in states where physicians can bargain with insurers under state supervision, under the state action doctrine. Passage of the Campbell Bill would provide these protections nationally. The Campbell bill, submitted to the US House of Representatives by Tom Campbell (R-CA), a former law professor at Stanford University, says that health care workers will be extended the protections of the labor laws negotiating with insurers. A second paragraph was added this year that says they cannot strike.

To protect physicians in the interim, the American Medical Association is helping self-employed physicians pursue disputes with insurers, hospitals and practice associations though its Private Sector Advocacy Group and the AMA Litigation Center. To date, the American Medical Association has helped physician groups from 24 states address their various concerns with payers, the most common of these dealing with claims payment and onerous managed care contracts. For public advocacy, the American Medical Association is highly effective, as shown by recent House passage of the Patient Bill of Rights.

Physicians need a variety of tools to protect their patients and practices in today's challenging environment. Physicians for Responsible Negotiation, the Campbell Bill and various private sector initiatives can help physicians stand up to payers in this brave new world of medicine. None of these efforts are any good, however, if they put our patients at risk. Physicians have a respected voice and we most use it intelligently. Our profession does not need, and our patients do not want, doctors to go on strike.

A moment in medical history

Before transfusion became established procedure

Between 11:00 AM and 12:00 noon on 20 May 1910, Thomas Addis transfused "about 300 cc of freshly drawn human phosphated blood" to a patient with hemophilia whose plasma clotting time was thereby shortened from 245 to 24 minutes (normal, 13 minutes). It was 30 minutes 2 days later, 32 at 4 days, 55 at 8 days, and 200 at 25 days.

Throughout 1910 Addis was a Carnegie research fellow at the laboratories of the Royal College of Physicians of Edinburgh, in Scotland. The transfusion was his only recorded foray in vivo; he was otherwise investigating the hemophilic abnormality in vitro. His methods with oxalated venous blood plasma were advanced, antedating Quick's "prothrombin time" (1935) and Brinkhous's "one stage partial thromboplastin time" (1950). He showed hemophilic blood to lack inhibitors, to have normal fibrinogen and thrombin, and its blood cells to have normal thromboplastic activity. Addis concluded controversially—but correctly—that the hemophilic defect lay in the plasma, but wrongly that hemophilic prothrombin abnormally resisted conversion to thrombin; however, "prothrombin" was still a hypothetical concept in 1910.

In 1890 chemicals binding calcium in blood were found to prevent coagulation, which could be restored by adding back calcium chloride. This helped clotting investigators greatly and by 1909 several were using potassium oxalate, although its use for blood transfusion was prevented by fears about toxicity and the resulting insoluble calcium oxalate. Phosphate also binds calcium—relatively weakly. In Edinburgh in the 1890s Brakenridge had transfused phosphated blood to people with pernicious anaemia. Addis presumably knew of this as he used the identical (rather concentrated) formula of one part 5% sodium phosphate to three parts blood. Phosphated transfusions had also been conducted by Braxton Hicks in the 1860s. Although Addis's procedure was experimental rather than therapeutic, the blood probably contained an effective dose of factor VIII.

Addis published this work only in 1916, after Ottenberg reported a similar experience with citrated blood. In 1910 even citrate was considered too toxic, although Todd and White had transfused citrated blood between cattle. In 1915 several reports led to citrate being rapidly adopted for human transfusions. Both Addis and Ottenberg were puzzled by other findings—Addis by an apparent efficacy of transfused serum, Ottenberg by a similar efficacy of sodium citrate by itself. Residual "thromboplastins" and "pyrogens" probably explain these effects.

Addis was not the first to transfuse a patient with hemophilia. Lane (1840) successfully transfused George Firmin, aged 11, after 6 days' postoperative bleeding, with "5 ounces" of blood; and Crile (1909) referred to three other episodes. Addis's donor, probably himself, and patient were presumably compatible serologically but no pretransfusion testing was recorded. Such precautions were still rare although Landsteiner had described the ABO groups in 1901. However, ABO frequency distribution among the Scots would have favored Addis.

Addis had hoped to complete his work before publication, but transfusion practice was not quite ready for wider application. Routine blood grouping and safe anticoagulant and preservative regimens came only with the tragic battlefields of the first world war. In 1911, aged 30, Addis emigrated to the new medical faculty at Stanford, California, where he specialized in renal medicine (describing the "Addis count" in urine) and gained a reputation for good teaching and scientific thoroughness. He died on 4 June 1949.

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Mail

Aspartame and breast and other cancers

To the Editors,

I discovered an extraordinary correlation between asparatame (marketed as Nutrasweet and in its generic form) and increasing breast and prostate cancer incidence.

My observation occurred while I was researching the metabolism of aspartame. Aspartame consists of phenylalanine, aspartic acid and methanol (wood alcohol). Upon metabolism, Nutrasweet breaks down into aspartic acid, a neuroexcitatory agent,[1] phenylalanine, an amino acid, and methanol. The methanol is converted to formaldehyde,[2] which then accumulates within the cells.[3]

Formaldehyde has been considered an inducer of cancer[4] and acts to alter DNA.[5,6] Thus, it seemed reasonable to superimpose a graph of breast cancer incidence against that of the rising use of Nutrasweet (aspartame).

Nutrasweet received limited approval for use as a sweetener in 1974, then further expansion in 1981 and unlimited approval in 1983. These points are marked on the curve of breast cancer increases obtained from the governmental surveillance statistics (see Figure 1).

A similar relation was found with prostate cancer. Interestingly, breast and prostate cancer rates are five to six times higher in Europe

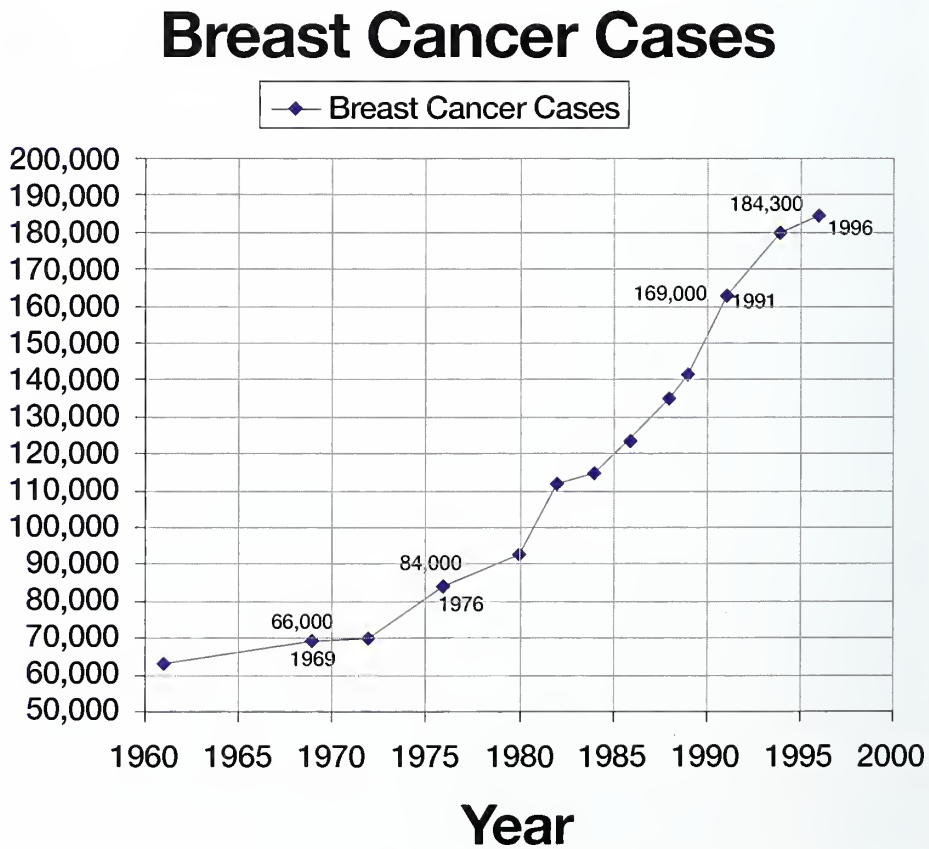

Figure 1 Illustration of breast cancer incidence based on government surveillance statistics

and North America than in Asia and Aftica, the latter correlating with lower use of Nutrasweet.[7,8] Also, review of the original Nutrasweet animal laboratory research findings released under the Freedom of Information Act revealed mammary tumors were observed in many of the animals.

The correlation associated with a likely mechanism of cancer induction in susceptible people points to a need for immediate scrutiny of aspartame as an environmental cause of many thousands of cancer cases.

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Response

The letter by Dr Schwartz has not taken into account some important information. It is true that aspartame consists of phenylalanine, aspartic acid, and methanol, but even among high consumers of aspartame, the relative contribution of these compounds is trivial, less than 10% of the average human intake of these compounds from regular diet[1,2]. Moreover, aspartame was not commercially available until 1981, so that the compound could not have been in the market in 1974.

With respect to the graph in Dr Schwartz's letter, it is well known that factors unrelated to each other, but having similar time trends, be these breast cancer incidence, aspartame intake, number of cars of a particular maker, or commercial air traffic, do demonstrate what is described here as extraordinary correlation. In epidemiology, we use the term ecological fallacy. The reported increasing incidence of breast cancer and prostate cancer in the United States may be due partly to the increased intensity of screening by mammography and prostate specific antigen (PSA), respectively, although early life influences may have contributed to the secular trends of breast cancer.[3] In any case, those who want to hazard etiological statements on the basis of these ecological data should also take into account several points, including the fact that incidence is a rate and should take into account the population at risk, that there is a latency involved in most etiological factors, including those with growth enhancing potential, and that the few analytic studies of artificial sweeteners in relation to breast cancer have yielded null results.[4,5] Perhaps even more important in this instance, is the fact that breast cancer incidence in the United States has been declining during the last few years.[3,6,7] It would be just as inaccurate to hypothesize that long-term use of aspartame reduces the risk of this cancer.

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Dr Trichopoulos is responding on behalf of Monsanto. Dr Trichopoulos' department receives research funding from Monsanto.

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Modern obstetrics and female life span

To the Editors,
Advances in pre- and perinatal care have significantly decreased the mortality of females such that now, in contrast to former times, the life span of women in the United States exceeds that of men (78.8 versus 72.4 years). To ascertain the effect of childbearing on females of a far lower creature who do not have the benefits of modern medical advances, my colleagues and I chose to study the fruit fly.

We selected Drosophila melanogaster of the type yellow forked attached and white apterous (Carolina Biological Supply Co, Burlington, NC*) because of ease of differentiation between the sexes and ease of handling. A virgin, newly emerged (less than 12 hr old) female and similar male fly were added to each of 100 4″ × 1″ vials containing 4 g of Instant Drosophila Mix* containing 10 ml of water and a few grains of yeast. The vials were kept in an incubator at 22° C, and the paired flies were allowed to mate and lay eggs for 15 days. The two parents were then removed.

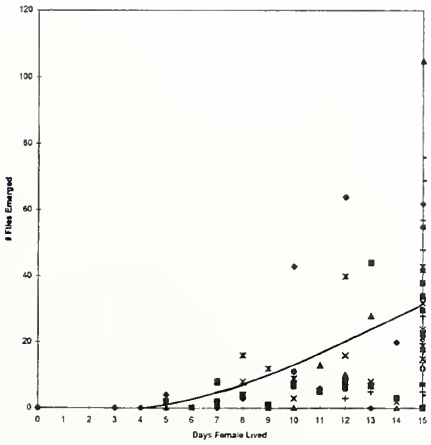

Figure 1 Number of flies emerged versus days female lived

During the 15-day interval, approximately twice as many females as male flies died (55 females, 33 males, p=0.0016). Indeed, we found that the mean life span of these flies was significantly shorter for the female than for the male during this interval (12.06 ± 0.49 versus 13.90 ± 0.29 days, p= 0.0019). After clearing, we counted (over an additional 2 weeks) the number of adult progeny flies that subsequently emerged in these vials. The data (Figure 1) show that females that live less than 15 days yield far less progeny than the heartier ones that were still alive on clearing day. These results indicate that child bearing does, indeed, take a toll on these primitive females and credit the obstetric advances that have alleviated this plight in human females.

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Original Research

Questionnaire survey of California consumers' use and rating of sources of health care information including the Internet

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ABSTRACT **Objective** To understand how Californians use and rate various health information sources, including the Internet. **Research design** Computer-assisted telephone interviews through which surveys were conducted in English or Spanish. **Subjects** A household sample generated by random digit dialing. The sample included 1007 adults (18+), 407 (40%) of whom had access to the Internet. **Main outcome measures** Past health information sources used, their usefulness and ease of use; future health information sources, which are trusted and distrusted; and concerns about integrating the Internet into future health information seeking and health care behaviors. **Results** Physicians and health care providers are more trusted for information than any other source, including the Internet. Among those with Internet access, a minority use it to obtain health information, and a minority is "very likely" to use e-mail to communicate with medical professionals or their own doctors and nurses, to refill prescriptions, or to make doctor appointments. Also, most of those with Internet access are "unlikely" to make their medical records available via the Internet, even if securely protected. **Conclusions** The public, including frequent Internet users, has major concerns about the confidentiality of electronic medical records. Legislation may not assuage these fears and a long-term, open and collaborative process involving consumers and organizations from all the health care sectors may be needed for full public assurance.

INTRODUCTION

Recent changes to the healthcare system include increased enrollment in managed care,[1] shorter visits with health care providers as services and costs are monitored,[2] and concerted efforts to move care from in-patient to out-patient settings.[3,4] These changes were occurring as the Internet was becoming a major channel for the sharing of information. These parallel developments have led to consumers taking more control of their own health care and the Internet becoming a major source for health information. Studies of health information source preferences are primarily conducted with specific patient groups[5-10] or as ways to improve specific source efficiency.[11] Proprietary information on consumer preferences is used to develop commercial web sites, but little public information is available.

The needs and behaviors of consumers surrounding health and health care information are frequently the subject of media articles,[12-15] and today's consumers are more informed and demanding as they take charge of their own health care.[16,17] An Institute for the Future report[18] describes the major forces pushing the Internet into health and health care as "strong" and "unstoppable." These forces include consumer demand, increasing consumer experience with e-commerce and e-mail, the ease of obtaining diverse health care information through the Internet, and the low-cost of disseminating information this way. Barriers to integrating the Internet into health and health care include concerns about privacy, weakness in browser and search engine technologies, uncertainty about the quality of information, and lack of universal standards for communications and transactions. Despite these barriers, people are increasingly using the Internet to obtain health-related information.

One survey puts the number of websites related to health issues at more than 15,000[19] generating thousands of hits each day. America Online, as a portal to healthcare sites, reports 2 million users regularly visit its healthcare site.[20] Others report that in 1998 more than 17 million US adults searched on-line for health and medical information,[19] and in 1997, "43% of the 40.6 million adults in the United States who used the Internet were seeking health information." This number is projected to grow to 30 million a year by 2000.[21]

Physicians and health care providers have traditionally been responsible for both providing health information and maintaining the confidentiality of medical information, and two recent polls confirm that they are the most trusted sources of health information.[15,23] This consumer trust remains, despite projections that millions of Americans will use the Internet for health information and the recognition that the Internet can provide emotional support groups for those with specific conditions.[16,21,22]

This study sought to understand how Californians use and rate various health information sources. Its hypothesis is that California households with Internet access will display different characteristics from those without access.

METHODS

The questionnaire was developed by the National Health Foundation and was reviewed by its Center for Health Information Technology Advisory Board. Survey questions centered on health information sources used during the past year, the usefulness and ease of using these sources, anticipated future sources, which sources are trusted, health information wanted, and demographics. Those respondents with Internet access were also asked about their willingness to integrate Internet use into future health-related activities.

Marketing Scientifically Inc. International administered the survey. The English language questionnaire was programmed into the company's computer-assisted telephone interviewing system that insures interviewing procedures and scripts are implemented identically to each respondent. After review and pre-testing, the questionnaire was translated into Spanish. The final questionnaire had 32 questions and took, on average, 20 minutes to complete. Each respondent chose to speak in English or Spanish during the interview. Household sampling was conducted using random digit dial methods from a database that excluded business, government, and university telephone numbers.

RESULTS

Data were collected from a total of 1003 households during August 1998, with 407 households having Internet access. The maximum sampling error for percentages based on the entire sample (n=1003) is ± 3.2%, and for the subsample (n=407), is ±5% at the 95% confidence level. The results are provided in four discrete areas: demographics; past health information sources, their usefulness and ease of use; future health information sources, which are trusted and distrusted; and the specific concerns of those with Internet access.

Demographics

Respondents were mostly female (63%), age 25 to 44 years (39%), and white (61%), with a mean annual income of $40,100. These data differ slightly from California demographics: females (50%), 25 to 44 year olds (47%), and whites (53%). Hispanics (sample 22%, statewide 28%) and Asian/Pacific Islanders (sample 6%, statewide 11%) were under-represented. Participants with Internet access were significantly more likely to be male and living in the suburbs and significantly less likely to be Hispanic, over 60 years old, and earning under $50,000/year ($p \geq .028$).

Past health information sources

In the past year, 471 (47%) of the respondents had sought health information for themselves or their families. Those with Internet access (56%) and women (52%) were significantly more likely than those without access (41%) and men (39%) to have sought information ($p \geq .001$). Although those with Internet access were more likely to have sought health information than those without access, only 37% of them used the Internet in their searches.

Physicians and health care providers were consulted by 85% of the respondents and were the single most important source of health information for all groups regardless of gender, ethnicity/race, age, or annual income. They were also ranked the most useful sources by the overall sample (74%) and by those with Internet access (70%). The Internet was ranked as the fifth most useful by both the overall sample (10%) and those with Internet access (19%). Although physicians and health care providers were the most useful sources of health information, they were not universally seen as being easy to access. Less than two thirds (64%) of the overall sample reported them as the easiest or second easiest sources to use. Overall, the Internet ranked as the fifth easiest source to use while those with Internet access ranked it third (Table 1).

Future health information and sources

Overall, 70% of respondents said they are most likely to consult their physicians and health care providers for information about medical conditions in the future. Those with Internet access, however, were significantly less likely to report using physicians and health care providers and more likely to report using the Internet ($p=.0001$). A total of 78% of the overall sample and 75% of those with Internet access report that physicians and health care providers are their most trusted health information sources. Those with Internet access ranked the Internet third, it was ranked fifth overall. Both the overall sample and those with Internet access ranked the Internet as the fourth most distrusted source (Table 2).

Issues for those with Internet access

A total of 407 (40%) people in the sample have access to the Internet from their homes (76%), offices (40%), schools (10%), and public access locations (4%). Over two-fifths (42%) go online everyday, although men (52%) are significantly more likely to do so than women (33%, $p=.002$). Almost three-quarters (72%) use e-mail, again with significantly more men (80%) than women (66%) using it ($p=.003$). Over one-half (56%) report having used the Internet to seek health information, but there are several concerns about further integrating it into their health care.

E-mail with medical professionals and personal physicians/nurses

Less than one-third (30%) reported that they anticipate "often" (9%) using or "most likely" (21%) using e-mail to ask a medical professional specific health questions. Forty-six percent, however, report "often" (15%) or "most likely" (31%) using e-mail to communicate with their own

Table 1 *Health information sources used in the past year*

Health information sources used in past year	Sources used		Useful		Easy to use	
	All % (n = 1003)	Internet % (n = 407)	All % (n = 1003)	Internet % (n = 407)	All % (n = 1003)	Internet % (n = 407)
Physician/healthcare provider	85	83	74	70	64	55
Family member/friend	34	45	28	27	34	35
Telephone advice line	10	12	6	7	5	6
Employee assistance program	22	24	10	10	9	10
Newspaper/magazine/ journal article	31	40	23	21	24	21
Advice book	32	36	18	20	20	22
Internet	19	37	10	19	13	24
Health fairs	10	8	3	1	9	1

doctors and nurses, with those persons going on-line every day most likely to report using this service "often" (20%).

Prescription refills and doctor appointments

When asked how likely they would be to use the Internet to order prescription refills and make doctors appointments, almost half (49%) anticipated "often" (18%) and "most likely" (31%) using this type of service.

Protected medical records

Respondents were more apprehensive about making their medical records available via the Internet than about using e-mail to communicate with their healthcare providers. They remain apprehensive even if their records are protected through encryption or some other means and even if they frequently used the Internet. Two-fifths (40%) are "not likely" to use this type of service, with 31% reporting they would "often/most likely" use it.

Privacy and confidentiality

Respondents had major concerns about the privacy and confidentiality of medical information being available to medical professionals even via a secure Internet connection. Over one-fourth (27%) had serious concerns and 25% stated they would "never" agree to release their medi-

Table 2 *Future health information sources*

Health information sources anticipated to be consulted in the future	Most likely to consult		Most trusted		Most distrusted	
	All % (n = 1003)	Internet % (n = 407)	All % (n = 1003)	Internet % (n = 407)	All % (n = 1003)	Internet % (n = 407)
Physician/healthcare provider	70	63	78	75	4	5
Family member/friend	9	10	8	8	34	32
Telephone advice line	2	1	1	0	13	13
Employee assistance program	2	1	1	0	4	4
Newspaper/magazine/ journal article	2	2	3	3	37	34
Advice book	6	8	3	5	4	3
Internet	5	13	2	5	11	12
Health fairs	1	1	1	0	6	6

cal records via the Internet, regardless of the security safeguards.

CONCLUSIONS

For more substantive analyses, such surveys must be repeated so that trend analyses can be conducted. Nevertheless, some specific findings have implications for how medicine and technology seek to meet consumers' health information needs. First, people trust their physicians and health care providers more than any other information source. Second, only a minority of those with Internet access are likely to use e-mail to communicate with medical professionals or their own doctors and nurses, or to refill prescriptions or make doctor appointments. Third, most individuals with Internet access are unlikely to make their medical records available via the Internet, even if protected through encryption or some other means.

Although legislation defining who controls access to medical information and what punishments pertain to improperly using it is necessary, it is probably insufficient to fully assure the general public. Full assurance probably requires a long-term, open and collaborative process involving consumers and organizations from all the sectors of health care.

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COMMENTARY

Rejoice and help patients get the best from the World Wide Web

We should rejoice in the findings of Pennbridge et al, patients still trust their physicians to provide the most credible answers to health questions. And, the Lady's Home Journal is still a distant contender. The World Wide Web is somewhere in between. The increasing role of the World Wide Web in patient education and medicine has a number of implications and poses several quandaries.

Educated patients are more able to participate in their own care and most providers see this as a positive. For the provider, however, a knowledgeable patient can be perceived as a two-edged sword. Patients with ready access to medical information are better prepared to question the care that we furnish. Have no doubt that patients may be more up to date on recent research than we are. Almost every illness has a presence on the web through a legitimate organization with an interest in keeping patients informed about recent developments.

This availability of information has several consequences. First, it is a good way to establish a dialogue with our patients. Some of the information on the web is misleading or incorrect, and patients may not be able to prop-

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erly interpret the information as it applies to their condition. Second, it may bring home the message that it is impossible to keep up with all of the latest in medicine. This realization may force us to frequently re-educate ourselves in response to patients' questions. The challenge to health care providers is to become as facile with the web as are our patients and to embrace it as a source of medical education. Services such as MD-Consult (www.mdconsult.com) provide almost instantaneous access to the full text of peer-reviewed journals and textbooks. There is no longer any need to make onerous and time-consuming trips to the library.

There is also an implied dichotomy in these results. Patients get information from their physician or from the web. This separation is artificial. There is no reason that we cannot harness the World Wide Web so that patients can get information from their physician by this same vehicle. We can act as a guide for our patients to help them avoid misinformation. It is impractical for each of us to develop our own compendium of online information. It is not beyond us, however, to develop a home page for our practices with links to reputable information sources (for example, American Cancer Society, Mayo Clinic, etc.). You can pick and choose particular advice from each site until you have a complete portfolio of patient information. You can also refer your patients to sites that display the Health on the Net (HON) logo. The HON criteria, which can be found at www.hon.ch/HONcode/Conduct.html, are, among other things, a voluntary attempt to protect patient privacy, to assure that qualified professionals are providing online information, and to make readers aware of any biases that a site may have (for example, commercial support). These steps will help, but not entirely ensure, that the information your patient is accessing is credible.

Among the dilemmas raised by the World Wide Web is what constitutes a physician-patient relationship in a virtual environment? Does giving advice by e-mail to an individual who is not a patient in your practice constitute a legally binding physician-patient relationship? If it does constitute such a relationship, are you practicing medicine without a license if you give e-mail advice to a patient who lives out of state? If a site answers patient questions and is making money from advertising, does this form a contractual arrangement between the site and the patient? The legal implications will, I am sure, develop over time.

Experiences of hospital care and treatment-seeking behavior for pain from sickle cell disease: qualitative study

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ABSTRACT **Objective** To investigate how sociocultural factors influence the management of pain from sickle cell disease by comparing the experiences of those who usually manage their pain at home with the experiences of those who are more frequently admitted to hospital for management of their pain. **Design** Qualitative analysis of semistructured individual interviews and focus group discussions. **Participants** 57 participants with genotype SS or S/β-thal (44 participants) or SC (9 participants); the status of 4 participants was unknown. 40 participants took part in focus groups, 6 took part in both focus groups and interviews, and 9 were interviewed only. Participants were allocated to focus groups according to ethnic origin, sex, and the number of times that they had been admitted to the hospital for the management of painful crises during the previous year. **Results** The relation between patients with sickle cell disease and hospital services is one of several major, nonclinical dimensions that shape experiences of pain management and behavior for seeking health care. Participants' experiences of hospital care show a range of interrelated themes that are common to most participants across variables of sex, ethnicity, and which hospital was attended. Themes identified included the mistrust of patients with sickle cell disease, stigmatization, excessive control (including both overtreatment and undertreatment of pain) and neglect. Individuals responded to the challenge of negotiating care with various strategies. Patients with sickle cell disease who are frequently admitted to hospital may try to develop long-term relationships with their caregivers, become passive or aggressive in their interactions with health professionals, or regularly attend different hospitals. Those who usually manage their pain at home expressed a strong sense of responsibility for the management of their pain and advocated self-education, assertiveness, and resistance as strategies toward hospital services. **Conclusions** The organization and delivery of management for the pain of a sickle cell crisis discourages self-reliance and encourages hospital dependence. Models of care should recognize the chronic nature of sickle cell disorders and give priority to patients' involvement in their care.

INTRODUCTION

The management of sickle cell disorders is of growing concern for health professionals and policymakers in the United Kingdom. Painful crises are the dominant feature of sickle cell disorders both for the person who is suffering and for service use.[1] In the United States, most painful episodes are managed at home,[2,3] and many patients with sickle cell disease do not normally use health services to manage pain.[2] Analysis of patterns of treatment seeking in the United Kingdom is hindered by the lack of coordinated information about the affected population.[4] Ongoing analysis of data on hospital admissions and estimated population figures, however, suggests that there is a similar pattern of service use to that in the United States, with a small percentage of the affected population consuming a disproportionate amount of resources. Most previous research has systematically excluded individuals who have infrequent contact with hospitals, assuming that they experience little or no severe pain.[5] Those who manage their pain at home have been similarly neglected by the organization of health services, which has focused on acute management rather than on primary and community care. Published research tends to ignore both the experiences of individuals who manage their pain in the community and the influence of nonclinical factors on treatment-seeking behavior.

Biomedical approaches to pain have traditionally conceptualized the experience of pain as fundamentally individual and purely biological.[6] Our investigation draws on the anthropological understanding that sociocultural factors influence the perception of, response to, and communication of pain.[7] Similarly, treatment-seeking behavior is a social action influenced by social context and individual meanings and experience; it is not simply a straightforward individual response to the experience of physiological symptoms. We aimed to compare the experiences of pain and its management in patients with sickle cell disease who had different frequencies of hospital admissions and to identify nonclinical factors contributing to patterns of service use. Given the lack of research on this issue, we have used mainly qualitative methods to gain insight into the range of possible factors influencing experiences.[8]

PARTICIPANTS AND METHODS

We used focus group discussions and semistructured individual interviews as our main methods.

Participants

We recruited 57 participants with sickle cell disease (hemoglobin type SS or S/β-thal or SC) across the greater London area using theoretical sampling (systematic, nonrandom sampling of participants possessing specific characteristics selected to aid the development of theory) via a wide range of channels (Table 1).[9] The main study groups comprised participants admitted to the hospital with a painful crisis 3 or more times in the previous 12 months and those admitted once or not at all.

Ethical approval for the study was obtained from the research ethics committee of St Thomas's Hospital, London. All participants completed consent forms before participating in interviews or focus groups.

Structured questionnaire

All participants completed a short, structured questionnaire to collect sociodemographic data (Table 2) and information on hemoglobin status, usual analgesic drugs, and current treatment (Table 3); participants then took part in an interview or focus group or both. Participants were asked how often they were admitted to the hospital and about painful episodes. The definition of painful episodes was similar to that used in previous studies: "pain that was in any part of your body, lasted at least 2 hours, you felt was caused by sickle cell, and may or may not have led you to go to hospital."[10]

Interviews

We conducted 18 semistructured interviews with 15 persons in settings chosen by the participants. Six pilot interviews were conducted before the focus groups to develop the topic guide. Ten interviews were conducted in parallel with the focus groups with persons who spent significant time in the hospital and who were unable to attend a focus group.

Focus groups

Participants were allocated to 1 of 8 different focus groups on the basis of information provided in the questionnaires;

Table 1 *Channels of recruitment*

	Number (%) of hospital admissions per year	
	3 or more (n = 28)	1 or fewer (n = 29)
Researcher visiting inpatients	9 (32)	0
Referral by counselor or specialist nurse	8 (29)	9 (31)
Snowballing*	3 (11)	1 (3)
Participant in previous research	2 (7)	2 (7)
Researcher visiting outpatient clinic	6 (21)	11 (38)
Media	0	2 (7)
Mailing	0	2 (7)
Referral by general practitioner	0	2 (7)

*Recruitment of further participants by networks of those already participating.

Table 2 *Characteristics of participants*

	Number (%) of participants (n = 57)
Ethnic origin	
West African	29 (51)
Afro-Caribbean	26 (46)
Other African	2 (4)
Sex	
Female	32 (56)
Male	25 (44)
Age (years)	
20–40	49 (86)
41–60	6 (11)
Missing data	2 (4)
Mean age	34

the composition of each group was determined by ethnic origin (African-Caribbean or west African), sex, and the number of times participants had been admitted to the hospital in the previous year (>3, or <1). Each group met for two discussions of 1.5 to 2.5 hours. The main topics discussed in the focus groups were diagnosis, childhood and adult experiences of pain, hospital experiences, primary care, analgesia, the anatomy of a crisis, employment and education, support and relationships, and identity and lifestyle. All focus groups were facilitated by 1 of us (K. M.; the only nonparticipant present), whose role was to introduce the topics, ask questions, and encourage participation by all group members. The facilitator aimed to maintain a balance between covering the intended topics and allowing for the introduction of unanticipated issues that participants deemed relevant.

Statistical analysis

We analyzed the data from the quantitative questionnaire using statistical software (Epi-Info, Version 6; Centers for Disease Control and Prevention, Atlanta, GA). The qualitative data consisted of the transcripts of interviews and focus group discussions. All qualitative data were professionally transcribed; the main researcher then checked the transcripts against the original recordings for accuracy and the inclusion of nonverbal detail (such as laughter, murmured assent, etc). Owing to the large volume of data, one of us (A. S.) did not listen to the recordings or participate in coding but read all transcripts and discussed the evolving coding framework at regular intervals. We used another software program for the analysis of the qualitative data (Nud*ist, Version 4; Qualitative Solutions and Research, Victoria, Australia). Coding categories were developed from the data rather than using a predetermined analytical framework. Text units (each uninterrupted segment of speech) were grouped together according to perceived common underlying themes. As coding progressed, each of these general themes was further subdivided as a greater understanding of the complexities of the data developed. The identification of horizontal relations between coding categories was a parallel process eventually leading to the development of an explanatory model, an aspect of which is presented here.

Validation

At the end of the study, information on the results of laboratory electrophoresis was obtained for most patients and compared with participants' self-reported hemoglobin status. The researcher also validated the accuracy of participants' reported pattern of admissions in those for whom there was any doubt by discussion with hemoglobinopathy counselors and staff at outpatient clinics.

RESULTS

Questionnaire results

Twelve London hospitals were named by participants as their base hospital; two participants reported regular attendance at several hospitals. Patients admitted infrequently were less likely to use strong opioids and more likely to use mild analgesics in the hospital (Table 3). The proportion requiring strong analgesics was 100% for those admitted three or more times each year compared with 72% for those admitted fewer than three times (95% confidence interval for the difference in the proportions between groups: 10%-46%). There was considerable overlap in the number of painful episodes between those admitted frequently and those who usually managed their pain at home (Table 3): half of those who managed their pain at home had experienced 10 or more painful episodes during the previous 2 years. Of the 51 cases in which self-reported results were compared with laboratory results, there was agreement in all cases of SS or S/β-thal (40 cases) and SC (9 cases). Two (of a total of 4) cases in which participants did not report or did not know their hemoglobin status were identified as being SS (both of these were patients who managed their pain at home).

Qualitative results

We identified sociocultural and psychological factors that, along with differences in clinical severity, might contribute to variations in the pattern of hospital use by persons with sickle cell disorders. We focused on two main themes: experiences of hospital care and strategies for the management of pain and treatment seeking.

Experiences of hospital care

Our findings related to general aspects of the hospital experience that were consistent for most participants, although a few had little experience of hospital care.

Table 3 *Hemoglobin status and treatment in the hospital by number of hospital admissions per year*

Variable	Participants (n = 57)*	Hospital admissions per year 3 or more (n = 28)	1 or fewer (n = 29)
Hemoglobin status			
SS or S/β-thal	44 (77)	24 (42)	20 (35)
SC	9 (16)	4 (7)	5 (9)
Unknown	4 (7)	0	4 (7)
Transfusions and hydroxyurea			
Transfusion ever	43 (75)	19 (33)	24 (42)
Transfusion regimen currently	4 (7)	4 (7)	0
Using hydroxyurea	5 (9)	5 (9)	0
Missing data	5 (9)	0	5 (9)
Usual drugs taken in the hospital			
Strong analgesia (pethidine, diamorphine or morphine, or a combination)	45 (79)	27 (47)	18 (32)
Not strong analgesia (no pethidine, diamorphine or morphine, or a combination)	7 (12)	0 (0)	7 (12)
Missing data	5 (9)	1 (2)	4 (7)
Number of self-reported painful episodes in previous 2 years			
1–2	2 (4)	0	2 (4)
3–10	17 (30)	5 (9)	12 (21)
11–20	12 (21)	4 (7)	8 (14)
21–30	8 (14)	4 (7)	4 (7)
>30	13 (23)	11 (19)	2 (4)
Missing data	5 (9)	4 (7)	1 (2)

*Values are numbers (percentages). Painful episodes do not add up to 100% because of rounding.

Mistrust

Participants gave accounts of mistrust by their professional caregivers. In all of the groups who were frequently admitted to a hospital (groups 1-4) and two of the groups who managed their pain at home (groups 5-8), participants described being suspected by health professionals of exaggerating pain:

"The doctor will look at you, and he goes, 'I don't think that you're in a lot of pain' " (focus group 1).

In contrast, some participants managing their pain at home described how health professionals seemed to suspect them of understating their pain:

"They get suspicious because they can't believe you can be better in 2 days, but if I can look after myself, I don't see why I should be there . . . I feel better, I can stop taking [the painkillers] . . . Once I didn't have [any] more pain, but they [were] giving me tablets which I didn't know [were] painkillers" (focus group 7).

Stigmatization

The perception of patients with sickle cell disease that they were treated differently from other inpatients was a prominent theme in all focus groups and interviews. Virtually all participants thought that patients with sickle cell disease were stigmatized as drug addicts: a stereotype that simultaneously feeds on and reinforces the mistrust of patients with sickle cell disease described above.

"The nurse turned around to me and said, 'It's not because we don't [want to] give you the painkillers, it's [because] we're scared that you're [going to] get hooked on it, and we don't [want to] see you down on the street hustling drugs' " (focus group 3).

Control

The issue of control was closely related to mistrust and stigmatization. Participants described various ways in which health professionals routinely exerted control over their care regimens and failed to involve them in decision making, particularly in relation to giving drugs (overtreatment as well as undertreatment of pain), hospital admissions, and discharge.

Patient: "They give me diamorphine [diacetylmorphine hydrochloride], but I try to take as small [an amount] as I can . . . sometimes they push."

K.M.: "They want you to take more?"

Patient: "Yes. They keep saying to me, 'Oh, the pain will come again.' And I say, 'When the pain comes, I will tell you' " (focus group 7).

Patient 1: "You do tend to find certain nurses who like to overstep their bounds, they feel they know the best regime[n] for your painkillers."

Patient 2: "Absolutely."

Patient 1: "They feel that you should be having less than . . . on the prescription . . . and they will try and

control your pain regime[n] to the way they think it should go" (focus group 2).

"They kept saying, 'I think we're going to send you home,' and yet, I knew it was the sort of chest pain that I should be in. . . . So there was this debate . . . in the end, I was right: it was sickle lung" (focus group 5).

Neglect

Participants spoke of the neglect of a range of needs, including personal care and monitoring of vital signs. Some participants related such neglect to wider issues such as understaffing, whereas others interpreted it as further evidence that patients with sickle cell disease were a low priority for health professionals. Failure to provide adequate psychosocial support was also included as an example of neglect, although this is a major issue that we can refer to only briefly here.

"[The nurses] just seem to concentrate on the pethidine [meperidine hydrochloride] injections, and that's it. I've been in days without having any assistance with my hygiene and personal care and changing of the sheets and helping me with fluids . . . just basic stuff like that" (from an interview).

"On [names ward], observations wasn't done. . . . If they come around and you're asleep, then they leave you. . . . Sometimes they've already written in what your temperature is, but the thermometer is still under your arm" (from another interview).

"You need to talk about what's bothering you, but that is not an issue when you go in hospital: they see that you've got sickle cell, and that's it. . . . I went into a state where I was practically suicidal, and nobody recognized nothing except that I had sickle crisis" (focus group 1).

Strategies for pain management and treatment seeking

The extent to which a person's relation to pain had been shaped by these experiences was variable, and each person responded differently to the challenges of negotiating the management of pain and general care. Those who normally managed pain at home used different strategies from those who were frequently admitted to the hospital.

Strategies of patients managing pain at home

The strategies used by patients managing pain at home were typified by two main characteristics: a sophisticated critical appraisal of hospital services, which acknowledged that spending time in the hospital was often not in the patient's own best interest, and a strong sense of self-responsibility for the management of the condition, which included a recognition of the power of mental attitudes.

Assertiveness

"People think, 'Oh, the doctor knows best,' but I think the patient knows best, because, really, if you don't believe in yourself, no matter what the doctors do, it's not [going to] help you. You have to have that self-power to say, 'Look, enough's enough.' Because how long are you going to carry on taking all these different drugs? How long are you [going to] keep on dealing with the side effects?" (focus group 7).

Self-education

"I think you do have to educate yourself because you'll be in wards where nurses have never seen a sickler—it didn't come up in their training—so I think it really comes down to you at the end of the day" (focus group 6).

Resistance

"I'd work during the day . . . in agony, go home . . . take the pethidine [meperidine] through the night, get up the next morning, go to work again without taking any drugs—in pain, agony—come home in the evening and repeat the same thing again. So you're always trying to fight with it" (focus group 6).

"It's good to try and have a positive mind, not 'Oh, the pain's here. I'm gonna just let it take over me,' not lie down in [the] hospital for weeks on end, getting them to drug you up 'til God knows" (focus group 7).

"Sometimes you want to fight it, and you don't want to go into [the] hospital, because you know what [the] hospital is, and you know what staying out of [the] hospital can do, and you know whether you're going to be better within 2 or 3 days of staying at home, hopefully, or you may be in [the hospital] a week or 10 days. So it's all about mental toughness" (focus group 8).

Strategies of patients frequently admitted to the hospital

Participants who were more frequently admitted to the hospital advocated the benefits of developing long-term relationships with caregivers in 1 hospital to receive more individualized care. This strategy may be thwarted by the high turnover of nurses and interns; some participants emphasized the significance of their relationship with their consultant/specialist as a bulwark against mismanagement and the unsympathetic attitudes of junior staff. A minority of the patients who were admitted to the hospital frequently resorted to verbal and occasionally physical aggression, sometimes provoked by the undertreatment of pain and poor communication with health professionals and at other times as an expression of unresolved anger. Others reported that they maintained a passive attitude in their interactions with their caregivers, which necessarily extended to their attitude toward their condition. Discharging themselves from 1 hospital and going straight to another in response to unsatisfactory care was a strategy used by a minority of patients.

Developing relationships
"If you're in a regular hospital where they know you . . . they tend to be able to build up some form of relationship because they've seen you before. So they know exactly how your crisis behaves, how you usually cope. They can work with you" (focus group 1).

Aggression
"Every time I come to [emergency], he [the intern] will send me home . . . . One day, he canceled my painkiller and said I would have to go home, and I said, 'Today I'm not going home.'. . . So I held him, and I punched him" (interview).

Passivity
"Whenever they [doctors and nurses] say anything to me that I don't like, I just let it go by . . . . Whatever they want to do, they can just do it to me" (interview).

Use of multiple hospitals
"I've been in many hospitals [names 5; laughter from group] . . . . If I go to the hospital and my pain's not controlled, I don't care if I die, I'll get out of that hospital and go somewhere else to get pain free or to control my pain" (focus group 3).

DISCUSSION

In our study, we used methods that facilitated the emergence of participants' own accounts of their experiences, with minimal imposition of a predetermined analytical framework. Our findings suggest how a person's management of pain may be affected by experiences of, and responses to, health services. This comparative approach found that there were similar experiences of hospital care in London, across variables of sex, ethnicity, and hospital attended. We also highlighted striking differences in attitudes toward hospital services between those who usually manage their pain at home and those who are admitted to the hospital more frequently.

Our investigation has been innovative in including individuals with sickle cell disorders who had previously been excluded from research: those who usually manage their pain at home. The knowledge that some persons with sickle cell disorders rarely experience severe pain suggests that those managing their pain at home may fall into this category. In the absence of an objective measure of clinical severity, we have used the self-reported frequency of painful episodes to measure pain in participants who were admitted to the hospital infrequently. This imperfect indicator relies on subjective recall over a significant period. We think, however, that taken together with participants' accounts and the fact that many of those who usually managed their pain at home were known to counselors or attended outpatient clinics (Table 1), these data provide evidence that home management is not simply a reflection of lesser disease severity. Although the patients who were admitted to the hospital more frequently reported a greater overall number of painful episodes, there was sufficient overlap between the two groups to show that they are not two clinically discrete populations. In addition, the two groups seemed to have a similar distribution of genotypes. Validation of patients' self-reported hemoglobin status (when known by patients) showed that there was complete agreement with laboratory records, suggesting that accurate information was provided by the study participants.

Hospital experiences and management of pain: explanatory model

Our participants' accounts of hospital care accord with previous research in highlighting issues of stigmatization, a lack of involvement in treatment decisions, and undertreatment of pain.[11-13] Our findings suggest a model that illustrates the implications of the relationship between health professionals and patients for the individual's management of pain (Figure 1). A pervasive mistrust of patients with sickle cell disease leads health professionals to exert excessive control over their pain management regimen. Other studies have found that a significant proportion of health professionals may subscribe to the stereotype of patients with sickle cell disease as drug dependent.[14,15] The undertreatment of pain from sickle cell disease has

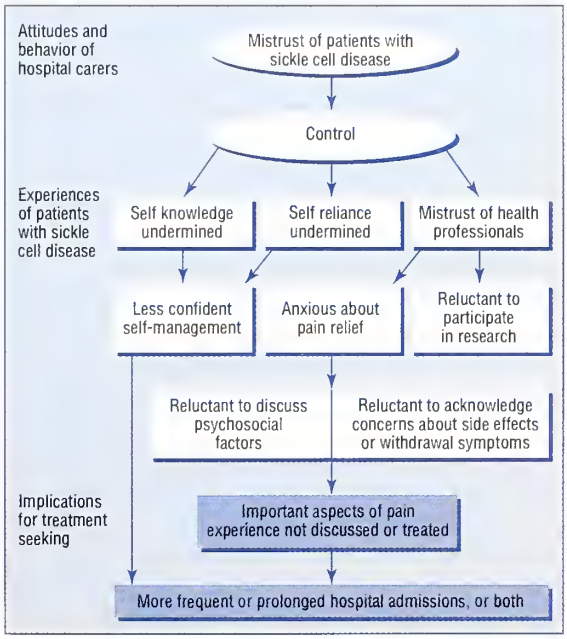

Figure 1 How hospital experiences may adversely influence individual pain management in patients with sickle cell disease

been described elsewhere[11-13]; our findings indicate that health professionals may also be overtreating pain, particularly in those patients who are only rarely admitted to the hospital. This observation suggests that the approach to treatment was not due solely to health professionals' concerns about addiction, but also related to more fundamental issues of trust, control, and the involvement of patients. Failure to involve patients with sickle cell disease in making decisions about their care undermines their self-reliance and self-knowledge, reducing their capacity for self-management.

Repeated experiences of control and neglect erode patients' trust in their professional caregivers, leading to considerable anxiety about receiving adequate pain relief. Ballas observed that "Patients with sickle cell disease often do not convey their true feelings about their management for fear of not receiving adequate treatment for pain."[16] Similarly, we found that patients may be reluctant to discuss certain issues, such as withdrawal symptoms and the influence of psychosocial factors on painful crises and hospital admissions, which they feared would diminish the validity of their entitlement to treatment in their caregivers' eyes. This mistrust of health professionals seems to have adversely influenced recruitment into research and clinical trials[17]; difficulties experienced in recruiting patients who were frequently admitted to the hospital for the current study were further evidence of this effect.

An understanding of the history of race relations in the United Kingdom prompts the question: to what extent do the experiences of mistrust and stigmatization of patients with sickle cell disease mirror the health care experiences of London's black population more generally? There is little basis for comparison owing to the paucity of published research on this issue, although alienation has been identified as a major theme in existing work.[18] In contrast, black British people's experiences of other public services such as education and policing have inspired far more published analyses, and it is reasonable to suppose that the health care experiences of black people might show parallel themes of institutional racism. Any degree of alienation characterizing the experience of a black person seeking treatment for a racially neutral condition is compounded in the case of a patient with sickle cell disease owing to the status of the disorder in the United Kingdom as a "black disease." This racialization may have contributed to the development of an inadequate policy response, underdevelopment of services and undercoverage of the condition in medical and nursing curricula (unpublished data).[19] All of these factors are probably significant determinants of the problems highlighted by our research.

Sickle cell disorder as a chronic condition

Recent models of chronic disease and disability emphasize the role of the social and political environments in perpetuating dependency.[20] Experiences of hospital care for pain from sickle cell disease may disempower patients, inhibit self-management, and actively contribute to dependence on acute care services, as our model illustrates. The implications become salient when this model is considered in the context of the underprovision of public services for sickle cell disorders: that is, the lack of primary and community care and the failure of policymakers in social services, education, and housing to acknowledge the special needs associated with this condition.[21,22] Thus, the path of least resistance leads to hospital dependency. Although our findings indicate that many of those affected have resisted this route, further work is needed to understand the factors contributing to such resistance; greater insight may also be achieved by comparison with other chronic conditions.

The status of sickle cell disease as a chronic disorder is inadequately recognized by policymakers and service providers. The management of chronic disease demands that health professionals and patients work in partnership,[23] whereas our findings indicate that pain management for sickle cell disease is based on the acute care model. Recent discussions about models of care for sickle cell disorders have frequently degenerated into arguments about the use of opioids for pain.[24,25] Commentators have failed to acknowledge either the complexity of the relationship between patients with sickle cell disease and health professionals or the attendant implications for the experiences of pain and treatment seeking. The use of principles of palliative care[26] and models of care for other chronic conditions[23,27] could enhance this discussion; of particular relevance are issues of communication, continuity of care and home care, intersectoral collaboration, and a holistic understanding of pain. Models of care for patients with sickle cell disorders should also be informed by the recognition of this population's diversity. The historical focus on the minority of the population with sickle cell disease who frequently use acute care services perpetuates both the stigmatization of service users by health professionals and bias in research and the organization of services.

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data analysis and the paper. D.B. contributed to the study design, discussed emerging ideas, and contributed to the paper. A.S. and K.M. will act as guarantors for the paper.

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COMMENTARY

Don't blame the patients

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It is estimated that about 70, 000 Americans have sickle cell disease. In a given year, only about 50% of this group will have even one episode of pain. Only between 1% and 3% will have six or more painful episodes, and a minority of patients seem to have severe pain almost constantly.

It is the minority of sickle cell patients who have frequent episodes of pain or nearly continuous pain who repeatedly seek treatment for their pain at hospital emergency departments and inpatient wards. They are difficult patients: they do not really get better, they keep coming back with the same problems, they are demanding, and worst of all, they want narcotic analgesics, drugs that physicians are uncomfortable about dispensing.

Because they engender such discomfort in their caregivers, these patients are generally not treated well. There is little evidence to the contrary; the literature is replete with articles describing, from the patient's viewpoint, inadequate treatment of pain, hostility, and implicit or explicit accusations that drug addiction rather than "real pain" was their problem. The patients interviewed by Maxwell and colleagues confirm this information.

The clinical spectrum of disease in sickle cell patients ranges from those with severe symptomatic hemolytic anemia and frequent crises to those who would remain undiagnosed but for routine testing. Although it is clear that a spectrum exists in the objective manifestations of sickle cell disease, such as extreme variations in the severity of anemia, aseptic necrosis of bone, and renal disease, we are uncomfortable that such variations in a "subjective" symptom such as pain should also be attributed to the disease. Because there is no demonstrable reason why one patient should have more pain than another and no way to demonstrate objectively that a patient actually has pain, physicians trying to understand the situation resort to a strategy of "blaming the victim." The entire difficult, frustrating situation can be explained by deciding that the patient is an addict and the (otherwise inexplicable) behavior is not due to pain.

Maxwell and colleagues compare two groups of sickle cell patients: a group that is seldom hospitalized for pain control and a second group that is hospitalized frequently. They try to discount the notion of a biological/medical explanation for this difference in behavior (more on that later) and look for sociocultural factors that might influence how these people manage their pain. In this attempt, they have not collected data on the social factors that might influence the patients' ability to manage their own care, such as income level, employment status, family structure, family support, or relationship with a primary care physician. Instead, they concentrate on coping strategies.

The authors report findings that sickle cell patients who are seldom hospitalized are "sophisticated" and display that admirable quality, a "strong sense of self-responsibility." Those who were frequently hospitalized have followed "the path of least resistance," which leads to "hospital dependency." The former are characterized by "assertiveness," the latter by the extremes of either "aggression" or "passivity." The terms chosen to describe the groups have strongly positive and negative connotations.

Patients hospitalized frequently for episodes of pain represent a difficult and complex clinical problem, which cannot be addressed by exhorting them to be more like their less troublesome peers. Their episodes of severe pain must be managed aggressively. Patients who have chronic pain must receive adequate treatment for pain, with daily narcotics as needed. Their psychiatric problems, including that of drug dependence when present, must be addressed, preferably with the help of a psychiatrist. They must have access to specialists for management of their frequent orthopedic, ocular, infectious, and renal problems. It may take a village to raise a child, but it certainly requires a well-coordinated team, with adequate support, to care for a patient with severe sickle cell disease.

The single most adaptive strategy described among frequently hospitalized patients is the attempt to develop long-term relationships with caregivers. Patients who need narcotic medications, must, if they are to manage their pain outside the hospital, have a physician who can help them do so and is willing to prescribe an adequate oral regimen of narcotics. It is nearly impossible for most of these patients to find such a physician: most are underinsured, most have difficulty with transportation because of poverty and physical handicaps, and many are socially disorganized as a result of poverty, chronic illness, and hopelessness. Many also have developed, as Maxwell et al point out, an aggressive (assertive) stance toward physicians and other caregivers.

When one adds to this mix the pervasive paranoia about narcotics, which leads to the reluctance of most physicians to prescribe significant doses of narcotics on a long-term basis to patients who do not have cancer, the problem is insurmountable. Patients are reduced to using emergency departments and inpatient hospital stays for pain management.

The authors acknowledge that our systems of social services and of medical care serve these patients poorly; needs for education, housing, transportation and dependable consistent primary care are not met. In spite of this acknowledgment, they have attempted to, and apparently believe they have succeeded in, identifying "responses to health services" among the seldom hospitalized that are adaptive and that, by implication, others would do well to emulate.

I believe they err in failing to acknowledge the most obvious possibility: that those who use the hospital for pain management do so because they have more severe pain, more often. Their own data show that the "frequently hospitalized" had many more pain episodes than the "seldom hospitalized."

It is also an error to look within the patients for correctable causes of "hospital dependency" without examining the obvious psychosocial influences, which might affect the choice to use the hospital. By examining the patients' "coping strategies" rather than their living conditions, we are looking for the pathology in the wrong place. To paraphrase Pogo, the enemy is not the patients, it is us.

capsule

Add water for weight loss Such is the exquisite precision of the body's appestat—which links energy requirements and satiety—that very small excesses in caloric intakes on a regular basis will result in considerable weight gain over time (*American Journal of Clinical Nutrition* 1999;70:448-455). Reducing the energy density of food by adding extra water during its preparation seems to be effective in enhancing its satiating effects: eat soup for lunch.

Research Digest

Bright light and high-density negative air ionization reduces symptoms of seasonal affective disorder

QUESTION

Do timed bright light and negative air ionization reduce symptoms in patients with seasonal affective disorder (SAD)?

DESIGN

Randomized, morning-by-evening light crossover trial balanced by parallel group controls in addition to a non-photic control (negative air ionization), with follow up to 4 weeks.

SETTING

Psychiatry department in New York.

PARTICIPANTS

A total of 158 patients between ages18 and 65 years with a DSM-III-R diagnosis of SAD were recruited through the media and physician referrals. Exclusion criteria included other Axis I disorders, a suicide attempt within the previous 3 years, and habitual sleep onset later than 1 AM or awakening later than 9:00 AM; 145 participants (92%) completed the study.

INTERVENTION

Participants were allocated to six groups for two consecutive 10- to 14-day treatment periods. Two parallel groups received morning treatment with negative ions. Four groups received light treatment and were crossed over at mid-point using the following sequences: morning-evening, evening-morning, morning-morning, and evening-evening (10,000 lux, 30 min/day). Two groups received negative air ionization treatment at either high density (2.7×10^6) or low density (serving as the placebo control, $1.0 \times 10^4 cm^3$) (high-high and low-low sequences, 30 min/day [AM]). All treatments lasted 20 to 28 days, with a 1- to 3-week withdrawal phase.

MAIN OUTCOME MEASURE

Symptom severity was assessed using the structured interview guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder version (SIGH-SAD).

MAIN RESULTS AND CONCLUSION

Data are reported for the 124 participants who had a relapse or who remained depressed during the withdrawal period to ensure that clinical improvement was not caused by spontaneous remission. Participants in the light treatment groups and the high-density negative air ionization treatment groups improved in percentage change scores on the depression scale. Bright light in the morning or evening and treatment with high-density negative ions led to reduction (>50%) in depressive symptoms in at least half of those treated (Table). Remission (defined as a SIGH-SAD score of ≤8 after treatment) rates were higher in the morning light, evening light, and high ions groups compared with the low ions group at week 4, and in the comparison of morning light with evening light (Table). Bright light and high-density negative ionization reduced depressive symptoms in patients with seasonal affective disorder.

M Terman, JS Terman, DC Ross. Arch Gen Psychiatry 1998;55:875-882.

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Treatment comparisons at week 4 for improvement in depressive symptoms and remission rates in seasonal affective disorder.*

Outcome	Morning light, evening light, high-density ions	Low-density ions	Relative benefit increase (95% CI)*	Number needed to treat (CI)*
Improvement in depressive symptoms†	67, 61, 55	26, 26, 26	153 (29 to 479), 131 (17 to 430), 109	3 (2 to 8), 3 (2 to 13), NS
Remission‡	56, 30, 40	5, 5, 5	972 (122 to 6014), 478 (15 to 3266), 660 (45 to 4394)	2 (1 to 4), 4 (3 to 30), 3 (2 to 11)
Outcome	**Morning light**	**Evening light**	**Relative benefit increase (CI)**	**Number needed to treat (CI)**
Remission‡	56	30	85 (12 to 214)	4 (3 to 21)

Values are percentages unless otherwise indicated. NS, not significant.
*Data provided by the author
†Change in SIGH-SAD score 50%
‡SIGH-SAD score #8

Commentary

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The treatment of winter depression (or SAD) is similar to that of other forms of affective disorder except that exposure to bright light has been recommended as the first-line treatment (directing visible light producing the intensity of at least 2500 lux toward the face). Indoors, at home, the intensity of light measured in front of the eyes of a standing person is typically; it is 300 lux to 500 lux at the workplace. Outdoors, illumination varies greatly by latitude, season, time of day, and local weather conditions. An overview of controlled trials with 332 patients showed that light of 2500 lux in 2-hour, daily morning sessions for 1 week led to improvement in 67% of patients with mild episodes of winter depression and in 40% with moderate to severe episodes.[1] Designs of trials of treatment with bright light have been compromised, however, by a lack of adequate control for placebo and blinding.

(cont'd p 316)

Bright morning light reduces depressive symptoms in seasonal affective disorder

AJ Lewy, VK Bauer, NL Cutler, et al. Arch Gen Psychiatry 1998;55:890-896.

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QUESTION

Is morning or evening light more effective in reducing symptoms in patients with seasonal affective disorder (SAD)?

DESIGN

Randomized, crossover trial with follow up to end of treatment.

SETTING

Sleep and Mood Disorders Laboratory in Portland, OR.

PARTICIPANTS

A total of 56 patients between ages 25 and 61 years, with a DSM-III-R diagnosis of SAD and a score of ≥20 on the structured interview guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder version (SIGH-SAD), were recruited through the media and by referrals from health professionals. Exclusion criteria included poor physical health, ideas or attempts of suicide, use of psychotropic medication, and other Axis I-III disorders. Five participants as well as 3 of 52 matched controls who participated did not complete the study.

INTERVENTION

Participants were allocated to bright light from either 6:00 AM to 8:00 AM or 7:00 PM to 9:00 PM for 2 weeks. After 1 week of withdrawal from light treatment, participants were crossed over to the alternate light schedule.

MAIN OUTCOME MEASURES

Symptom severity assessed using the SIGH-SAD scale and dim-light melatonin onsets.

MAIN RESULTS AND CONCLUSION

During treatment, SIGH-SAD scores for patients in the morning light group decreased twice as much as scores for patients in the evening light group. Remission (defined as ≥50% decrease in SIGH-SAD ratings to a score after treatment of ≤14) occurred in 19 patients receiving morning light compared with 3 patients receiving evening light (Table). Morning light advanced the dim-light melatonin onset and evening light delayed it both in participants and controls. Participants were delayed compared with controls at all assessment points in the study. Bright morning light reduced depressive symptoms in patients with seasonal affective disorder.

Morning light versus evening light in patients with seasonal affective disorder (treatment duration of 2 weeks)

Outcome	Morning	Evening	Relative benefit increase (95% CI)*	Number needed to treat (CI)*
Remission	37	6	533 (119 to 1831)	4 (3 to 7)

Values are percentages
*Calculated from data in article

(Commentary continued from page 315)

The studies by Terman et al and Lewy et al overcome some of these problems by their design and confirm that treatment with bright light is effective and well tolerated in patients with winter depression. The results of Terman et al and from another study[2] supports evidence that morning treatment with bright light has an antidepressant effect that can produce a greater number of full remissions. Both studies show that treatment with bright light is more effective when given in the morning than in the evening. A preliminary finding reported by Terman et al is the antidepressant effect of high-density negative air ionization.

Why is treatment with bright light effective in winter depression? Fixed-phase delays in the timing of the circadian clock have a key role in winter depression. The efficacy of morning treatment with bright light is related to corrective phase advances. The circadian cycle seems to be more elastic, however, in people with winter depression as compared with healthy people, deviating more from 24 hours and peaking at less regular times.[3] Patients with winter depression tend to display an abnormal degree of phase advance during treatment with bright light,[4] although the necessity of phase advances for clinical efficacy have now been questioned.

Some evidence suggests that the resetting of the circadian clock is worsened by the decreasing photoperiod or exposure to cold weather at high latitudes, and with aging. Separate time-givers may regulate waking up and falling asleep. Information on the direction (decreasing or increasing) and velocity of change of the photoperiod is being transformed into the production of melatonin. This signal might then train the two time-givers discordantly, predisposing to winter depression, for example, because of irregularities in the circadian clock.

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Family disadvantages in early life are associated with depression in adulthood

QUESTION

Are family disadvantages in early life associated with major depression in adulthood?

DESIGN

Population-based birth cohort study (Newcastle Thousand Family Study).

SETTING

Newcastle upon Tyne, UK.

PARTICIPANTS

Of 296 eligible participants (50% women), 266 were selected from a random sample of participants in the Newcastle Thousand Family Study during their first 5 years of life and then were assessed when they reached age 33 years.

ASSESSMENT OF RISK FACTORS

Six categories of family disadvantage were assessed: marital or family disruption, parental physical illness, poor physical care of child and home, social dependence, family overcrowding, and poor mothering (poor maternal coping skills). Multiple disadvantage was used to define those who had ≥4 coexisting criteria of family disadvantage in their first 5 years of life.

MAIN OUTCOME MEASURES

Depressed mood or major depressive disorder (MDD) according to DSM-III-R criteria.

MAIN RESULTS AND CONCLUSION

Altogether, 10.3% of participants were depressed at follow up. Multiple disadvantages in early life were associated with depression (odds ratio [OR] 5.1, 95% confidence interval [CI] 2.1 to 12.0). More women than men had depression (OR 2.7, 95% CI 1.1 to 6.3). Types of disadvantages associated with depression were social dependence and overcrowding (OR 5.1, 95% CI 2.1 to 12.0), poor physical care and poor mothering (OR 3.4, 95% CI 1.4 to 7.8), and family or marital instability (OR 3.0, 95% CI 1.3 to 6.7). Independent risk factors for depression were multiple disadvantages at age 5 years ($P<0.001$) and being female ($P<0.05$) (Table). Specific disadvantages that were independent risk factors for depression were family or marital instability ($P<0.05$); social dependence combined with overcrowding ($P<0.05$); and poor mothering combined with poor physical care ($P<0.05$) or female sex and poor physical care ($P<0.05$) (Table).

Table Associations between disadvantages in early life and depression

Risk factors	Adjusted OR (95% CI)*
Multiple disadvantages at age 5 years	2.2 (1.4 to 3.4)
Female gender	1.6 (1.0 to 2.5)
Family or marital instability	1.7 (1.1 to 2.8)
Social dependence and overcrowding	2.0 (1.2 to 3.3)
Poor physical care and poor mothering	3.1 (1.0 to 9.1)
Poor physical care, poor mothering and female gender	1.8 (1.1 to 2.9)

OR, odds ratio; CI, confidence interval.
*Adjusted for sex and types of disadvantages.

H Sadowski, B Ugarte, I Kolvin, et al. Br J Psychiatry 1999;174:112-120.

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Commentary

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The study by Sadowski et al provides strong evidence for the association between multiple adverse childhood experiences and adult depression. The identification of risk and of protective factors for major depressive disorder can point to ways of intervening before the onset of the disorder. Understanding the mechanisms by which family disadvantage in early life is linked with MDD remains an ongoing challenge.

Sadowski et al ask why do only some respondents exposed to early life disadvantages develop a disorder? Note, however, that the main outcome was 1-year prevalence of MDD; they did not measure the lifetime prevalence of the disorder. Given the episodic nature of MDD, many more participants may have had 1 episode of MDD before age 33 years. Understanding the pathways between predictors and outcomes over 27 years is a complex task. As Rutter and Rutter state, most processes of risk and protection do not happen at one point but involve a series of chain reactions over time.[1] Ideally, more frequent data collection in longitudinal studies will allow examination of continuities and discontinuities in exposure and outcome. Furthermore, data on the family history of MDD are essential in exploring how disadvantages in early life interact with genetic vulnerability in predisposing to the disorder.

What can we hypothesize about early childhood interventions to prevent later depression? Developing ways to provide economic and family stability for children seems important. Indeed, reducing instances of "poor mothering" and "poor physical care" may hold the most promise for early intervention. Olds et al showed that prenatal visits and early childhood visits to the home by nurses can prevent parenting problems and improve child health among disadvantaged families.[2]

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Traditional child psychotherapy does not reduce psychopathology when compared with academic tutoring

B Weiss, T Catron, V Harris, et al. J Consult Clin Psychol 1999;67:82-94.

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QUESTION

Is traditional child psychotherapy effective in reducing child psychopathology?

DESIGN

Randomized, unblinded, controlled trial with up to 3 years of follow up.

SETTING

Six public elementary and middle schools with socioeconomically disadvantaged children in Nashville, TN.

PARTICIPANTS

A total of 160 children participated (mean age 10 years, 63% boys, 55% African-American) with psychopathology and their families (54% headed by a single mother, 23% by two biological parents, mean number of children in home 2.7). On the basis of the Teacher Report Form (TRF), children had scores in the borderline clinical range for anxiety, depression, or both (41%); aggression (65%); attention problems or hyperactivity (60%); delinquency (57%); somatic problems (25%); and being withdrawn (47%). These children were not, however, clinically referred. Altogether, 86% of the children were included in ≥1 of the previously listed domains, and 60% were included in ≥2 domains. Follow up was 83%.

INTERVENTION

Children were allocated to child-oriented psychotherapy (n=76) or academic tutoring (n=84). Psychotherapy was given for up to 2 years by 1 of 7 therapists who selected which treatments and modalities to use; the mean number of sessions was 60 for individual therapy, 4 for group therapy, 13 for consultations with school personnel, 1 for psychiatric consultation and 18 for parent sessions. Children in the control group received a mean of 53 tutoring sessions of 45 minutes in duration. Children were treated in their schools.

MAIN OUTCOME MEASURES

The main outcome measure was a variant of the Target Problems Scale (TPS), which uses reports from parents, teachers, peers and self-reports. Child psychopathology was also assessed by other parent report measures (Child Behavior Checklist and Brief Symptom Inventory); teacher report measures (TRF and Teacher Behavior Questionnaire); peer report measures (Peer Report Measure of Internalizing and Externalizing Behavior); self-report measures (State-Trait Anxiety Inventory for Children, Vanderbilt Depression Inventory and Child School Behavior Questionnaire); and academic grades and school attendance. Children and their families were assessed at 6, 12 and 18 months and at 1 year after the end of treatment. Peer report measures were not included in the assessment at 1 year. Parents were given a consumer satisfaction survey at the 1-year assessment.

MAIN RESULTS AND CONCLUSION

No differences existed between groups in TPS scores or other psychopathology outcomes. Parents of children in the psychotherapy group reported greater overall satisfaction and a greater perception of change in mental health problems than did parents of children in the academic tutoring group.

Commentary

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The most frequently used treatments in clinical practice are those based on general tenets of psychodynamic, relationship and family therapy, which are often combined as an eclectic intervention. Weiss et al make a major contribution by conducting a large-scale evaluation of treatments as practiced with multiple outcome measures and meticulous evaluation of the results. The findings support previous work suggesting that evidence does not exist to support the effectiveness of the treatments most commonly practiced in clinical settings.

Researchers and practitioners will no doubt quibble about the fact that this is not a study of clinical patients in a clinical setting. Also, the evaluation is hampered by the use of a combination of many different treatments, sometimes given to the same child. There is no treatment called "traditional therapy"; specific treatments that are not merely lumped together need to be evaluated.

For the practitioner, the findings raise a key question: under what conditions ought one to use the treatments evaluated in this study? For many of the problems of children and adolescents (for example, anxiety, depression and conduct disorder) there are now evidence-based treatments.[1] Clearly, one of these ought to be used long before resorting to the treatments included in this study. Over 550 forms of psychotherapy are now in use for children and adolescents.[2] For most of these, there is no evidence of effectiveness.

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TOPICS IN REVIEW

Vaccines in the 21st century

see also p. 363

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Vaccination against infectious diseases has literally transformed the planet. It has succeeded in the elimination of smallpox and the near elimination of polio as scourges of humankind. This kind of success, as well as the great increase in understanding of immunology and the development of new technologies, has increased the hope that new vaccines will target other diseases. Indeed, expectations have been raised so much that vaccines are now being developed not just to prevent infectious diseases but to cure them. In addition, some conditions have now been shown to be related to infectious diseases—for example, human papillomavirus infection has been implicated in cervical cancer and Helicobacter pylori in gastritis, peptic ulcer disease, and stomach cancer—and vaccines should help to prevent or treat these diseases. Other clinical diseases or conditions are also now considered within the purview of vaccines. These include cancers (even those without a known infectious etiologic component), allergies, autoimmune diseases such as diabetes, metabolic diseases such as hyperlipidemias that lead to atherosclerosis and coronary artery disease, and even addictions such as cocaine and nicotine dependencies.

An examination of the recent advances in immunology and vaccinology provides insights into future vaccine developments. Great strides have been made in understanding how the body distinguishes self from non-self—that is, how the immune system recognizes a pathogen as being foreign and hence a target for killing. This is likewise important for understanding why the immune response sometimes becomes too active, resulting in allergies or autoimmune disease. By understanding which cells become activated and knowing what the triggers are, we can try intentionally to stimulate, alter, or suppress the responses.

The elucidation of how immune system cells process and then recognize and respond to antigens derived from pathogens has prompted the development of new technologies to try to mimic or even improve on these responses. Thus, whereas most existing vaccines were made simply and successfully by administering the pathogen in a weakened, killed, or dissected form, new approaches are much more "surgical." That is, they attempt to induce specific types of immunity (particularly cellular responses or particular classes of antibody) and against selected structures, rather than against the whole virus or bacterium or those parts that could easily be purified. In addition, the ability to sequence the genome of whole organisms has provided a new tool for identifying which proteins from a pathogen to include in a vaccine. Additionally, more effort is being applied to generating specific regional immunity at the site most relevant to prevent either infection (for example, mucosal surfaces) or disease.

Possibly the most intriguing revelations have been in the field of cellular immune responses—specifically, insights into how T cells recognize their targets and what occurs to the antigen in the target cells to make it into a form that can activate T cells. It has been recognized that a number of pathogens, for which we do not have vaccines, as well as immunotherapies for cancer, would require the generation of these T cells to prevent, limit, or treat disease. Earlier vaccine technologies may not be effective for generating these responses or may be considered problematic from a safety perspective for a given disease. For example, although live attenuated virus vaccines are quite effective for a number of diseases, they may in some instances revert to wild type virulence (for example, polio). Thus, using an attenuated HIV strain as a vaccine for HIV is considered by many to be too risky. Armed with an increased understanding of what is required to generate T cell response, "vaccinologists" have focused on finding ways to deliver antigen specifically to activate these T cells.

Summary points

- New vaccines are being developed for treatment as well as prophylaxis
- Elucidation of how immune system cells process and then recognize and respond to antigens has prompted the development of new technologies to try to mimic or even improve on these responses
- New approaches try to induce specific types of immunity against selected structures rather than the whole virus
- Researchers are also trying to find ways of delivering antigen specifically to activate the body's T cell response
- Efforts to harness the immune response and turn it in another direction are also being used to make vaccines for allergies, autoimmune diseases, metabolic diseases, and addictions

TECHNOLOGIES

Thus, insights into disease etiology and pathogenesis and the development of new technologies that enable vaccinologists to capitalize on new immunologic insights have been critical for this effort in new vaccines. Specific examples of new vaccine developments are given below as illustrations of various issues.

Recombinant DNA technology

The first example of a technology that has had an impact on vaccine development is recombinant DNA technology. Cloning has enabled the production of an effective hepatitis B vaccine that does not require the manufacture or purification of the intact or infectious virus. Other molecular biology tools have made it possible to identify which proteins are conserved among different strains of a virus or bacteria, or which are responsible for virulence of pathogens or oncogenesis in tumors. These proteins may be good candidates for vaccines.

Molecular attenuation of pathogens

Recombinant DNA technology has further resulted in the ability to manipulate genes so that, rather than relying on blind serial growth of viruses or bacteria in an effort to weaken them for use as live vaccines, pathogens can be attenuated or altered molecularly so that they are unable to effectively replicate or cause disease. For example, BCG is a live mycobacterium used in many countries as a vaccine against primary tuberculosis, but its effectiveness varies widely. This is partly because of the different derivations of different vaccine strains. Certain mutants, such as auxotrophic mutants, have been made through manipulation of the Mycobacterium tuberculosis genome, which results in the production of strains that cannot replicate unless they are provided with particular nutrients that would not be present in a human.[1] Likewise, salmonella and shigella strains are being attenuated molecularly so that they will still infect via the mucosal route, but will not be able to replicate.[2] Thus, by eliminating precisely and molecularly the pathogenicity from the pathogen, new vaccines may be made safer and more effective.

Vectors

Furthermore, a gene from a pathogen can be inserted into an innocuous agent so that the antigen can now be delivered in the form of a gene via an unrelated and non-pathogenic virus or bacteria. This technology is being used for attenuated versions of BCG, Salmonella, and Shigella. Vaccinia and a bird version of pox virus are also being evaluated as vectors for delivering the gene of a heterologous virus (notably HIV) in continuing clinical trials.[3]

A new type of vector that should enter clinical trials in the next few years for HIV and hepatitis C virus is based on the class of positive stranded RNA viruses known as alphaviruses.[4] These vectors provide several attractive features. They replicate by making multiple copies of mRNA encoding the structural proteins. Thus, when used as a heterologous expression vector, they cause the cell to make large quantities of the protein antigen quite rapidly. The replicon particle seems to be a normal viral particle on the outside, and hence can use some of the strategies that the wild-type virus uses for infecting cells efficiently. However, its genome has been altered so that the cell can produce the antigen for the vaccine but not the replicon structural proteins, and thus the cell cannot make any progeny virus. These particles, when made from certain strains of alphavirus, have the capability of targeting specialized immune cells called dendritic cells, which function to present antigen to stimulate cytotoxic T lymphocytes.

DNA vaccines

DNA vaccines, which are simply a bacterial plasmid encoding an antigen, are an even simpler form of gene vaccine that has been developed recently. These DNA vaccines have entered into clinical trials for a number of diseases such as HIV, malaria, and cancer.[5] DNA vaccines have generated considerable interest because they are simple and there is no need to make an intact virus or bacterium. Efforts to increase their potency are ongoing.

METHODS OF DELIVERY

Live poliovirus vaccines administered orally are the greatest current example of a practitioner- and user-friendly, economically feasible, and clinically effective vaccine. Given all of these attributes and the fact that most pathogens enter the host via a mucosal surface, vaccine development efforts have focused heavily on finding ways of delivering many types of antigens to the mucosa with and without the use of a live organism.

A new vaccine for influenza is based on the development of influenza strains that grow well only in the cooler temperatures of the nasal passages, but do not replicate in the warmer lower respiratory tract. This vaccine has been shown to be effective in children and adults after intranasal administration.[6,7] Non-living systems utilizing adjuvants (such as molecularly attenuated toxins from bacteria) are also being developed. An example of this is LTK63, a heat labile toxin of Escherichia coli, which has been made recombinantly with specific mutations to eliminate its toxic ability.[8,9] It has none of the toxic activity of the native protein, yet is a powerful adjuvant when coadministered with antigens in preclinical studies.

Oral delivery is an even more attractive route of administration from the patient's perspective, and several approaches are being developed. One approach has been to encapsulate the vaccine in such a way that it survives the gastric passage and reaches the intestine, which is rich in immune cells. In addition, some of the live attenuated organisms (such as Shigella and Salmonella described above) that normally invade the intestinal epithelium are being tested both as vaccines and as delivery vectors for antigens from other pathogens.[10-13]

An approach that has great appeal in relation to the potential ease of both production and delivery is using

transgenic edible plants to make vaccines. For example, genes encoding antigens have been cloned into potato plants. The potato makes the protein, and hence by eating the potato, animals—and more recently humans—have been shown to develop immune responses.[14,15] The drawback of using potatoes is that they are usually eaten cooked, and this may denature a protein antigen. Thus, bananas are considered the ideal food base for a vaccine. Of course, fundamental questions still need to be addressed, since intestinal administration of some antigens in certain forms has proved to be an effective means of generating antigen-specific tolerance. But the appeal of making an edible vaccine, especially one that infants would enjoy receiving, is great. Another advantage is that agricultural production will probably be less costly than biological manufacturing.

One of the functions of skin has been presumed to be protection from direct entry of entities (whether pathogens or compounds) into the body. Yet, the transdermal patch has been an efficacious and patient-friendly means of delivering systemic drugs. Vaccines of the future may be delivered through the skin by patches or other needleless devices.[16] These approaches would not only provide an advantage from the recipient's perspective but also may be able to harness the wealth of antigen presenting cells in the skin.

Adjuvants

Adjuvants are compounds that increase the immunogenicity of a given vaccine. Alum has long been the only compound approved for human use, but a vaccine with an adjuvant known as MF59 was licensed recently.[17] In the future, MF59 and other compounds still in development (for example, LTK63, see above)[8,9,18] will be used even more widely to reduce the number of immunizations or increase the potency in people who otherwise would not respond.

CLINICAL TARGETS FOR VACCINES

Infectious diseases

There are still many diseases for which we need vaccines or better vaccines. The misuse of antibiotics has resulted in the increasing development of antibiotic-resistant strains of bacteria. Furthermore, as useful and effective as antiviral drugs have been, their limitations have been painfully obvious for agents such as hepatitis C virus and HIV, where the side effects or rigors of the treatment regimen, or both, reduce the number of people who are treated. Other problems, such as the cost of treatment and the limited population of patients who respond, also underline the continued need for vaccines. In addition to the future development of successful vaccines for pathogens such as HIV, hepatitis C virus, malaria, and herpes simplex virus, new vaccines will be made that will be more effective against pathogens such as M tuberculosis, for which a vaccine already exists. In addition, although all vaccines to date have been for prophylaxis, vaccines will be developed to treat infectious diseases. For example, since the immune response is clearly capable of clearing infection for a number of pathogens that can also cause chronic infection, it is logical to try to stimulate such a therapeutic immune response in individuals who have not succeeded to clear infection on their own. Examples of such vaccines under evaluation include ones for hepatitis B virus, hepatitis C virus, HIV, tuberculosis, and human papilloma virus infections.

Cancer

Cancer gene therapy in the future will probably include the gene-based delivery not only of anti-angiogenic molecules but also of tumor-specific antigens in conjunction with cytokines. Therapeutic cancer vaccines illustrate how the concept of vaccines has widened to encompass non-infectious diseases and treatment. Furthermore, cancer vaccines illustrate the increasing blur between the areas of gene therapy and vaccines. The vectors used for so-called gene vaccines, which consist of either a DNA plasmid or of a viral vector only, are also being used for some gene therapies.

Allergies

Efforts to harness the immune response and turn it in another direction are also being used to develop vaccines for allergies. For example, a type 2 T helper response (the production of cytokines such as interleukin 4 and interleukin 10, which are necessary for making antibody responses) versus a type 1 T helper response (cytokines such as interleukin 2 and γ interferon, which are particularly relevant for cellular responses) to particular antigens has been implicated in the pathogenesis of certain allergies and autoimmune states. Thus, vaccines are being developed to specifically manipulate the antigen-specific response to be predominantly a type 1 T helper response.

Other conditions

While gene therapists work toward curing diabetes through gene therapy, vaccinologists are striving to prevent or treat this and other autoimmune diseases by efforts to induce antigen-specific tolerance and by altering the immunologic milieu to change the type of immune response.

Chronic and metabolic diseases such as hypercholesterolemia are now targets for vaccine development. The prevention of pregnancy via vaccines has been an effort in many countries because of the long duration of immunity seen with traditional vaccines. Another new arena is the

treatment of addictions, such as smoking and drug misuse, via the generation of immune responses against nicotine and cocaine, for example.

SOCIAL FACTORS

Social factors have also had an impact on vaccine development. For example, more effort is being made to eliminate the need for syringe injections, in an effort to make vaccines both more accessible in parts of the world and more acceptable from the patient's perspective. Likewise, the knowledge that each year millions of children worldwide die from infectious diseases for which vaccines exist, has spurred efforts to make more stable vaccines that do not need refrigeration or devices for delivery. And finally, the very success of vaccines at eliminating untold morbidity and mortality and the increased understanding of immune responses have raised expectations to desire prevention or cure of a myriad of diseases in addition to infectious diseases. The proved value of vaccines, coupled with powerful new technologies, promise that they will have an increasing role in efforts to improve the health of the denizens, both human and animal, of the planet.

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Sensors in medicine

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Sensors are devices that detect physical, chemical and biological signals and provide a way for those signals to be measured and recorded.[1] Physical properties that can be sensed include temperature, pressure, vibration, sound level, light intensity, load or weight, flow rate of gases and liquids, amplitude of magnetic and electronic fields, and concentrations of many substances in gaseous, liquid, or solid form. Although sensors of today are where computers were in 1970, medical applications of sensors are taking off because of advances in microchip technologies and molecular chemistry.[2,3]

Sensors have played an important role in many industries, providing the mechanical "vision" used for counting, sorting, reading, and robotic guidance. Tactile sensors, typically piezoelectric materials, generate voltage when touched, squeezed, or bent, or when their temperature is changed. Other sensors can detect specific chemical pressures and fluid levels. Cars, homes, and offices are loaded with sensors. In the short term, sensors used in medical applications will emit a signal that can be read at the point of determination or transferred by wire or wireless transmission to remote locations. Advances in microprocessor technologies have created a smart sensor that unites sensing capability and data processing in a single integrated circuit chip. The next step is combining sensing and processing with an actuator, such as microelectromechanical systems.[4,5]

SENSORS AT THE FOREFRONT

Many sensor technologies used in industry can be applied in medicine, and in the future, as unique sensors and sensor dependent microelectromechanical systems are designed and tested, non-medical industries will adapt them for industrial applications. Within the medical world, there is a broadening intersection between information technology and biotechnology, and increasingly the role of sensors, signal transducers, actuators, and micromachines will broaden too. Some examples of new generation medical sensors indicate new roles that these devices will have in many areas of health care:

- A subcutaneous system for the continuous monitoring and recording of tissue glucose concentrations in diabetic patients has just been approved in the United States. The next generation of implanted glucose sensors will give continuous values that can be read from remote hand held devices or desktops[6-8]
- One glucose sensor that looks like a watch sits on the skin and produces small electric shocks, which open up pores so that fluid can be extracted to monitor tissue glucose concentrations[6]
- Engineers for the Japanese company Toto have designed a toilet that analyses urine for glucose concentrations, registers weight and other basic readings, and automatically sends a daily report by modem to the user's physician
- A new microtool can measure anatomy and movement in three dimensions using miniaturized sensors (18 mm × 8 mm × 8 mm), which can collect spatial data for the accurate reconstruct of ultrasound images of the heart, blood vessels, stomach, and other organs
- A closed loop device (VIA Medical, San Diego, CA) is now available for blood analysis of neonates in critical care units. Through an indwelling line blood is circulated through a chemistry sensor, analyzed in a minute, and returned, with no loss of blood to the neonate
- Scientists have developed a lightweight fully automatic system for the detection of biological weapons. This system uses fluorescent antibodies, diode lasers, fiberoptics, and photodetectors to find airborne bacteria[9]
- Pathogens can also be detected by another biosensor, which uses integrated optics, immunoassay techniques, and surface chemistry. Changes in a laser light transmitted by the sensor indicates the presence of specific bacteria, and this information can be available in hours
- An Australian team has developed a highly stable and sensitive biosensor, which operates by switching the ion channels in a lipid membrane. When activated, biological receptors such as antibodies and DNA convert a chemical event into an electric signal. One team reports it could measure the increase in sugar content of dropping one sugar cube into Sydney harbor
- The next generation of cardiac pacemakers will become "smart" by receiving readings from various places in the body, such as oxygen saturation in the blood and cardiac wall pressure, allowing the pacemaker to adapt the heart's pacing to those real time readings[10]
- Polymer wafers can be saturated with therapeutic agents, such as drugs or insulin.[10] In the latter case, the wafer contains an enzyme that enables the wafer to change the pH and solubility of the insulin in response to changes in blood glucose concentrations. Smart wafers being tested on animals use magnetism or ultrasound to alter the dose of drug or to switch to another drug
- Scientists and engineers at Johns Hopkins Institute have developed a biochip photosensor, which can be implanted in the eye as an artificial retina for patients with macular degeneration and retinitis pigmentosa[10]
- Bacteria causing ear, nose, and throat infections can be instantly identified by an electronic "nose" that detects and differentiates the odors of growing bacteria[11]
- More than 20,000 people worldwide have been implanted with auditory sensors that bypass the nonfunctioning parts of the hearing mechanism. The first device that successfully interfaces with the human brain has become totally implantable with a battery that is digitally programmed and rechargeable by a portable inductive charging unit.[12]

Summary points

- Sensors are all around us
- Now sensors are moving into health care
- Leading the way are sensors for the monitoring of glucose and vital signs
- Sensors will change the site of health care
- Smart sensors will initiate an appropriate response, including treatment

IMPLICATIONS

To say that sensors will have a transforming effect on health care overstates their impact in the short term but is realistic within 10 years. Sensor technology will move the place at which health care is delivered in the future, chang-

ing the roles of hospitals, outpatient sites, homes, and ambulatory programs outside the home.

Hospital

The vent on the ceiling of the lobby will be an air monitor, which detects and reports any visitor who might transmit an airborne infection to a patient. Other sensors will be located in sinks for staff and visitors who are required to wash their hands before and after going into a patient's room. Any carrier will be swept with a handheld biosensor,[13] which identifies the specific organism and its sensitivity pattern.

The central laboratory will no longer exist. Less frequent tests will be done at a regional facility. The bacteriology laboratory will have been replaced by handheld biosensors, some of them functioning as electronic noses and others detecting and characterizing organisms in sputum, urine, and other secretions. The biochemistry laboratory will be gone too and replaced by chemical sensors worn by or implanted in every patient. For acutely ill patients, similar arrays of chemical sensors will be components of infusion catheters and beds. Values can be read by authorized staff on devices at any site.

The table used in operating rooms, the gurney, and the hospital bed will be the same piece of equipment, which will be wheeled around by robots. A sophisticated life support for trauma and transport unit (LSTAT, Northrop Grumman) designed for use under battlefield conditions and commercialized after the turn of the century, was the forerunner of this mobile bed. The apparatus combines aerospace materials, information processing, and integrated systems technologies in a unit that is capable of autonomous function. Through the use of embedded sensors the bed can monitor vital signs and blood chemistries, and it is also equipped to provide, under the control of sensors, mechanical ventilation, suction, intravascular infusion, and cardiac defibrillation.The patient can remain on this unit for surgical procedures and for recovery, while being continuously monitored by smart sensors that can activate homeostatic programs in response to changes in the patient. A central intensive care unit will no longer be needed for monitoring patients who are acutely ill or who have had surgery, reducing the risk of cross infection.

The cardiac catheter laboratory will have entered the age of molecular cardiology. Because pharmaceuticals have reduced the incidence of atherosclerosis and can dissolve plaques and clots, the number of patients requiring coronary angioplasty has dwindled.[14] Instead, catheters directed by sensors will be used to deliver angiogenesis factors and cultivated myocardial cells to ischemic and damaged heart muscle. A few patients are being treated with new sensor-based micromachines that can remove plaque from coronary arteries.[15]

Integrated Medical Systems Inc/Northrop Grumman Corporation

Northrop Grumman's life support for trauma and transport unit, which was designed to be used on the battlefield, uses embedded sensors to monitor a patient's vital signs

OUTPATIENT SITE

Patients provided with smart pacemakers, artificial retinas, and chemical sensors will be seen in a local ambulatory primary care clinic. The physician or nurse will obtain information on line about a patient's blood chemistries, electrocardiogram, blood pressure, and temperature. A diabetic patient will have had no diabetes-related problem since having a smart glucose sensor or insulin reservoir system implanted. An elderly woman with transfusion-related AIDS who seems healthy will be managed by a smart viral count sensor integrated with an implanted reservoir containing a drug. A smart sensor or drug reservoir system will be equally effective in the management of a patient whose dysfunctional manic depressive illness is now modulated by chemical sensors that detect the initial chemical imbalance and actuate the injection of appropriate drugs.

Home health care

Telemedicine and sensor technologies will have moved the outpatient laboratory and the doctor's surgery into the living room. Interactive video conferencing, educational programs, and a broad range of sensors will provide health care at a distance. Patients will not need to tell nurses their weight because it, vital signs, and blood chemistry values will be seen by the nurse on a handheld device. The nurse will be able to inform patients whether their toilet reported bacteria in their urine, and the pharmacy will deliver a prescription accordingly.

Ambulatory treatment

Smart blood pressure sensors will manage the drugs for patients with hypertension, sending an immediate alert to the central monitoring unit when integrated sensors for

cardiac function and vital signs indicate an unexpected problem. Episodes of diarrhea in patients with an irritable bowel syndrome will be detected as they begin to evolve and patients will be able to terminate these abruptly by pressing a drug-filled subcutaneous reservoir.

FINAL THOUGHT

Within 10 years, biosensors will cause changes in sites of care and the configuration of delivery systems. In many cases, the quality of care will be improved and patients can be managed in their homes. Hospitals will operate differently, as well as more safely and efficiently. These advances will, however, be expensive and in many parts of the world irrelevant. New and better vaccines for preventing common conditions afflicting many millions throughout the world would be a far greater benefit to mankind than all the sensors that will be developed and manufactured in the next decade. The contrast between the upper socioeconomic classes with access to sophisticated medical technologies and the lower socioeconomic classes that continue to bear unnecessary morbidity and mortality underscore eliminating health inequities as one of our highest priorities.

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Are we providing doctors with the training and tools for lifelong learning?

Medical practice is evolving rapidly as new information supplants old. Gone are the days when newly graduated doctors were armed with most of the information they would need for a lifetime of practice. Today's clinicians are required to be lifelong learners so that they continue to adapt to the changing ecology of the medical environment. Are our educational systems preparing doctors for this role?

LEARNING TO LEARN

Learning and developing competency in medicine is a little like running a bakery. We begin our medical education by having professors and teachers stock our empty shelves with new "loaves" of information. We, of course, do all the heavy lifting—the actual learning—to get this information onto the shelves, but our teachers are always there to tell us what bread to stock and what to do with it.

People who are good at "stocking their shelves" with information given to them by their teachers make good medical students. They excel in school and perform well on tests. They become expert at storing the right answer on their shelves, ready to pull it down when the question comes up in the examination.

Information overload

Many doctors become frustrated, however, when they find that the skills that allowed them to excel in the classroom, and even as house officers, are of little use in their medical careers. They have learned much, but they have not learned effectively how to learn.[1,2] The skills that got them through the pedagogical process are of little use when they are faced with a flood of information.[3] No one is there to direct them toward the new information they need to learn or how to identify those pieces of their hard earned knowledge that are no longer correct.[4,5] Unlike in a bakery, their loaves of information are not tagged with expiration dates.

This information overload can also be a handicap, since it sets up prejudices and biases that prevent us from embracing new ideas.[4] This shutting out of new information causes us to see the world in one, constrained way. When the only tool available is a hammer, everything looks like a nail.

Except for problem-based learning,[6,7] the traditional "lecture and test" method of teaching arms the learners with plenty of information, but does not give them the skills to update and replace this knowledge. One result is the inability of continuing medical education to affect the

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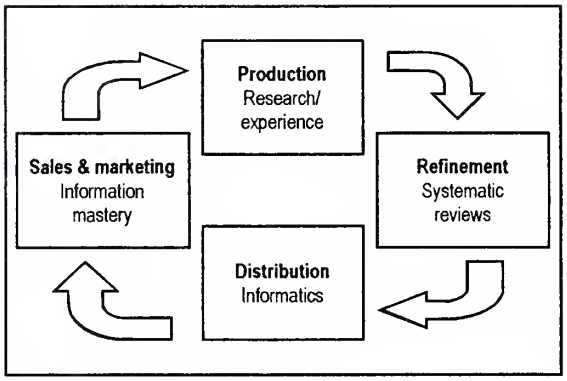


Figure 1 The information process.

actions of doctors.[8] Consequently, we have plenty of smart, learned people with inadequate training in how to continue to learn.

Paradox of adult learners

This is a problem. Educators faced with adult learners who are overwhelmed with information yet underskilled in learning are caught in a paradox. On the one hand, adults are self directed and make their own decisions, from what to eat to what to learn. This is the psychological characteristic that differentiates them from children. Yet when these adults are placed in a learning environment, they immediately revert back to the role into which they were conditioned by the pedagogical model—that of passive dependency on the teacher. If the educator treats them as child learners, though, the deeper need to be self directed reasserts itself, putting the educator in a teaching purgatory.[9]

The inability of the traditional, pedagogical techniques to prepare doctors for lifelong learning has been recognized for some time.[10-12] However, new technologies are now available that, in theory, allow learners to teach themselves. Rapid access via computers and database storehouses puts information at everyone's fingertips. Not enough attention has been paid, however, to the actual delivery process.

Summary points

- "Lecture and test" teaching methods arm learners with plenty of information but not the skills to update and replace it
- Although computers put information at everyone's fingertips, insufficient attention has been paid to how this information is delivered
- Traditional evidence-based medicine focuses primarily on identifying and validating written information; this is unrealistic and too time consuming for most doctors
- Efforts to increase the use of the best available evidence at the point of care must focus on the relevance of the information to patients and clinicians
- Doctors need a first alert method—a bulletin board—for relevant new information as it becomes available and a way of retrieving the information about which they have been alerted

PROVIDING THE GOODS

The medical information process (Figure 1) is analogous to the production of petrol for consumers. Placing the best information into the hands of the doctor (and the patient) at the point of care demands four distinct components :

- Production—clinical experience and original research produces the crude oil that begins the process
- Refining—this raw material must be refined before it can be used. In the medical information process, refinement occurs through systematic reviews and overviews, meta-analyses, decision and cost analyses, and guidelines
- Delivery—the informatics process then brings the refined product to the market, delivering it to doctors with ever-increasing efficiency. Too often, however, this informatics process is akin to trying to fill a tea cup with a fire hose
- Sales and marketing—the crucial component of the medical information process is the final step—educating the consumer about the product

Sales and marketing

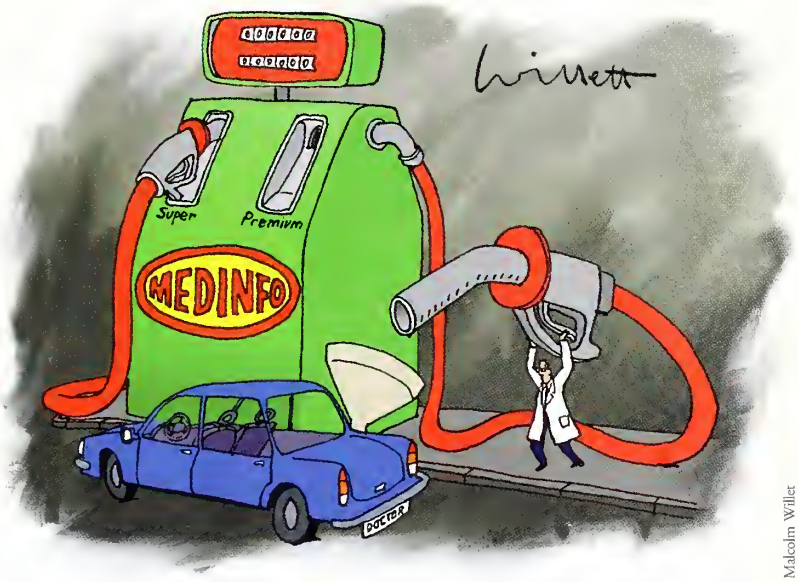
This last process, sales and marketing, has largely been ignored. The consumers of medical research are left to stumble on new information, essentially on their own. In the business world, manufacturers first make sure their new products are tailored to the needs of potential customers and then provide them with education on the benefits and use. However, most new research findings in medicine are rarely marketed to the consumers who need them the most (except for those that benefit the pharmaceutical industry).

EVIDENCE-BASED MEDICINE

Evidence-based medicine has been hailed as the long awaited bridge between practice and research. Simply put, practicing evidence-based medicine involves trying to use the best evidence currently available when making decisions about the care of individual patients. By defining precisely the clinical question and then searching and critically appraising current information, the doctor will be armed with the best evidence that he or she can then use to make a clinical decision.[13] Although the techniques of evidence-based medicine have greatly enhanced and simplified the evaluation of the validity of clinical research, they are not tailored to the day to day needs of practicing clinicians.

Filter needed

The traditional evidence-based medicine technique of information management begins by focusing on a specific, patient-related question. Though busy doctors are often faced with hunting for answers to practice generated questions, this problem-driven mode of information gathering is incomplete. Providing the best information at the point of care also requires an efficient method for foraging through the jungle of medical information to keep up with new findings–it demands a filter to find the relevant stuff.



Malcolm Willet

GETTING RESEARCH INTO PRACTICE

Traditional evidence-based medicine has focused primarily on identifying and validating information communicated by the written word, making it unrealistic and too time intensive for most clinicians. This approach of "rigor over relevance" is rooted deep in the foundation of pedagogy.[14] Clinicians, even those who identify themselves as practicing evidence-based medicine, infrequently use information sources that provide research in its pure form.[15] As a result, information from research that should change practice often does not achieve this, at least until it gets repackaged in a way that can reach and be understood by doctors. Although doctors report that they often use journals to obtain medical information, observation of information gathering habits has found that other sources, from pharmaceutical representatives to consultants, are more commonly used.[16-18]

Keeping abreast of research

Using research reports can be dangerous if they are not reviewed in their entirety. An isolated study, taken out of context, becomes medical "gossip" if doctors are not aware of other conflicting data.[19] Clinicians using the research reports must be kept up to date with the continuing context of the conversation with some sort of bulletin board that provides all of the available, relevant information.

PATIENT-ORIENTED EVIDENCE THAT MATTERS

Marketing efforts aimed at increasing the use of the best available evidence at the point of care must focus first on the relevance of the information to patients and clinicians. Doctors, as adult learners, will seek out new information and retain it only when they have the "need to know."[9] The best information for clinicians focuses on well-validated evidence that shows a direct benefit to patients. People desire to live lives that are long, functional, pain ftee, and symptom free, and the most relevant information addresses directly these goals. Two other criteria also are important. The information must relate to a problem that is common to the doctor's practice. Most important, though, the information must cause the clinician to change his or her clinical behavior.

We have coined the acronym "POEMs" (patient-oriented evidence that matters) to describe information that is of clear relevance to doctors.[19] Limiting our information gathering to a continuing search for POEMs can keep us from getting lost in the information jungle.

Bulletin board

Two specific tools are needed to help doctors identify efficiently information that is highly relevant and valid. Clinicians need a first alert method—a POEM bulletin board—for relevant new information as it becomes available. The myriad newsletters, web-based systems, and other current awareness services attempt to fill this need. With few exceptions, they do not filter information based on relevance and validity, and thus may not provide clinically useful information.[20-22]

Fast and portable retrieval

Clinicians also need a way of retrieving rapidly the information to which they have been alerted, but which has not yet been cemented into their minds.[23] Computer-based sources are available that can provide information in less than 30 seconds.[24] Hand-held portable computers that can be used at the point of care will probably be even more useful sources.[25]

HUNTER AND FORAGER

Medical schools equip future doctors with some of the information they will need to practice effectively. The traditional curriculum does not ensure that they become informed consumers of medical information who are capable of finding, evaluating, and applying new information as it becomes available. To be lifelong learners, doctors have to rely on new methods of learning while caring for patients, by using tools that help them to hunt and forage through the jungle of information.

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Pharmacogenomics

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We all differ in our response to drug treatment—occasionally with dramatic effects. The era of "one drug fits all patients" is about to give way to individualized therapy matching the patient's unique genetic make up with an optimally effective drug.[1] Pharmacogenetics and pharmacogenomics are the emerging disciplines that are leading the way towards individualized medicine.[2,3] Initially, researchers focused their attention on pharmacogenetics—variations in single candidate genes responsible for variable drug response. Subsequently, studies involving the entire human genome broadened the scope of investigation, giving rise to pharmacogenomics as one of the "hottest" fields in biotechnology today.

PHARMACOGENETICS

Unexpected drug reactions have been noted for some time, but the systematic study of hereditary origins began only in the 1950s. A few patients developed prolonged

Summary points

- Response to drug treatment can vary greatly between patients; genetic factors have a major role in treatment outcome
- Pharmacogenetics and pharmacogenomics are emerging disciplines that focus on genetic determinants of drug response at the levels of single genes or the entire human genome respectively
- Technologies involving gene chip arrays can determine thousands of variations in DNA sequences for individual patients; most variants are single nucleotide polymorphisms
- Pharmacogenomics aims at establishing a signature of DNA sequence variants that are characteristic of individual patients to assess disease susceptibility and select the optimal drug treatment
- This approach has the potential to revolutionize prevention and treatment of diseases

respiratory muscular paralysis after being given succinylcholine, a short acting muscle relaxant widely used in surgery and electroshock treatment. In the 1970s, a trial with the antihypertensive agent debrisoquin resulted in a precipitous drop of blood pressure and collapse in nearly 10% of volunteers. Furthermore, isoniazid therapy for tuberculosis caused peripheral neuropathies in patients who were sensitive to the neurotoxic effects of the drug. Ground breaking genetic and biochemical studies by Werner Kalow and others showed that these adverse effects result from polymorphisms in genes encoding the drug metabolizing enzymes serum cholinesterase, [4] cytochrome P-450, [5] and N-acetyltransferase. [6] These observations laid the foundation for pharmacogenetics.

Functional analysis

Today, many examples of genetic variability in drug response and toxicity are known (Table 1). In a few cases, genetic tests are beginning to find their way into clinical practice. In cancer chemotherapy with thioguanine, severe toxicity or even death can result if a patient is unable to inactivate the drug. Functional assays of thiopurine methyltransferase in red blood cells or genotyping can identify those patients who are at risk and must be given a much lower dose of thioguanine.[7,8] This is particularly critical for the 1 in 300 patients who is homozygous for null alleles (non-functional) of the gene encoding thiopurine methyltransferase which converts the drug to its inactive methylated form. Therefore, genotyping or functional

Table 1 Examples of inherited or acquired variations in enzymes and receptors that affect the drug response[23]

Protein	Phenotype	Drugs	Modified response
Enzymes			
Plasma pseudocholinesterase	Slow hydrolysis of certain esters	Succinylcholine	Prolonged apnea
N-acetyltransferase	Slow, rapid acetylators	Isoniazid Procainamide Dapsone Sulfadimidine, sulfasalazine, p-aminosalicylic acid, heterocyclic amines (foot mutagens)	Slow: toxic neuritis, lupus erythematosus Disease susceptibility Slow: bladder cancer Rapid: colorectal cancer
Thiopurine methyltransferase	Poor thiopurine methyltransferase methylators	6-mercaptopurine, 6-thioguanine, azathioprin	Bone marrow toxicity, liver damage
Dihydropyrimidine dehydrogenase	Slow inactivation	5-fluorouracil	Possible enhanced toxicity
Aldehyde dehydrogenase	Fast, slow metabolizers	Ethanol	Slow: facial flushing Fast: protected from liver cirrhosis
Catechol O-methyl transferase	High, low methylators	Levodopa, methyldopa	Low: increased response
Cytochrome P-450 subtype CYP 2D6	Ultrarapid* Extensive* Poor metabolizers	Debrisoquin Sparteine Phenformin Nortriptyline, dextromethorphan, etc	Poor: increased toxicity Extensive: lung cancer? Rapid: drug resistance
Cytochrome P-450 subtype CYP 2C19	Poor, extensive hydroxylators	Methoin, hexobarbitone, omeprazol, proguanil, etc	Poor: increased toxicity; ineffectiveness (proguanil)
Receptors			
β_2 adrenoceptor	Enhanced downregulation	Salbutamol	Poor control of gasping, wheezing in asthma
5-HT2A serotonergic receptor	Various polymorphisms	Clozapine	Associated with variable efficacy
HER2	Overexpression in breast and other cancers	Trastuzumab (Herceptin)	Overexpression associated with therapeutic efficacy
Transporters			
Multiple drug resistance transporter	Overexpression in cancer	Vinblastin, doxorubicin, paclitaxel, etc	Drug resistance

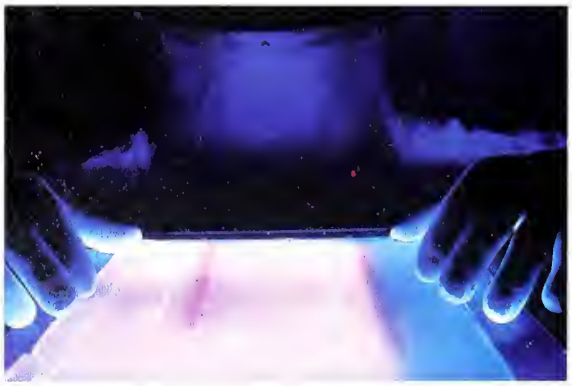
*Hyperactivity can result from activating mutations or gene duplications.

analysis has become standard practice in major cancer treatment centers such as the Mayo Clinic in Rochester and St Jude Children's Research Hospital in Memphis.

Cytochrome P-450

The large family of cytochrome P-450 genes has been most intensely studied because it contains the main drug metabolizing enzymes encoded by numerous genes.[2] Among the cytochrome P-450 subtypes, CYP2D6 and CYP2C19 play a critical part in determining the response to several drugs. This is particularly important for lipophilic drugs—such as drugs that act on the central nervous system and penetrate the lipophilic blood-brain barrier—because renal excretion is minimal and cytochrome P-450 metabolism provides the only means of effective drug elimination. Thus, homozygous carriers of CYP2D6 null alleles and cannot readily degrade and excrete many drugs, including debrisoquin, metoprolol, nortriptyline, and propafenone.[9] These patients are termed "poor metabolizers" for CYP2D6 selective drugs. Because of this they are exquisitely sensitive to these drugs. The incidence of "poor metabolizers" varies greatly among ethnic groups, ranging from 1% in Japanese to 15% in Nigerians. Similarly, patients with defective CYP2C19 subtypes are highly sensitive to methoin, hexobarbital (hexobarbitone), and other drugs selectively metabolized by this P-450 isoform.

The principal molecular defect in poor metabolizers is a single base pair mutation (A→ΠG) in exon 5 of CYP2C19.[10] Gene chips designed to test for polymorphisms of the main subtypes of cytochrome P-450 are now commercially available, but not yet in general clinical use. Cytochrome P-450 polymorphisms also affect the inactivation or, in some cases, activation or toxification of xenobiotics, and thus affect an individual's susceptibility to environmental toxins. This is studied in a field of research called toxicogenetics. Launched recently by the US National Institute of Environmental Health Sciences, the environmental genome project aims at understanding genetic factors in individual responses to the environment and parallels the study of genetic variability in drug response.[11]



VolkerSteger/SPL

Drugs will be fitted to genotypes

PHARMACOGENOMICS

As a scientific discipline, pharmacogenetics has made steady progress, but the human genome project has shattered any complacency as it has revealed profound gaps in our knowledge. By broadening the search for genetic polymorphisms that determine drug responses, the new field of pharmacogenomics begins to supersede the candidate gene approach typical of earlier pharmacogenetic studies. Initially hailed by pharmaceutical biotechnology as the latest trend in biotechnology, pharmacogenomics is now taken seriously everywhere. While genomic techniques serve to identify new gene targets for drug research, and some might refer to this as pharmacogenomics, the broader consensus is that pharmacogenomics deals specifically with genetic variability in drug response. The distinction between pharmacogenetics and pharmacogenomics remains blurred, but here are some of the new ideas typical of pharmacogenomics.

Searching for responsible genes

Each drug is likely to interact in the body with numerous proteins, such as carrier proteins, transporters, metabolizing enzymes, and multiple types of receptors.[1] These proteins determine the absorption, distribution, excretion, targeting to the site of action, and pharmacological response of drugs. As a result, multiple polymorphisms in many genes could affect the drug response, requiring a genome-wide search for the responsible genes. We now know that that there are thousands of receptor genes in the human genome, many of which are closely related to each other because they have evolved by gene duplications. Therefore, we must anticipate that a drug rarely binds just to a single receptor but rather interacts promiscuously with several receptor types. Chlorpromazine, for example, is known to engage several dopaminergic, adrenergic, and serotonergic receptors. As a result, polymorphisms in multiple genes can affect the drug response.

Polymorphisms

Polymorphisms are generally defined as variations of DNA sequence that are present in more than 1% of the population. Most polymorphisms are single nucleotide polymorphisms (referred to as "snips"). As the human genome contains three billion nucleotides, and variations between individuals occur in ~1/300 base pairs, around10 million single nucleotide polymorphisms probably exist. Only 1% of these may have any functional consequence at

all, and thus individuals differ from each other genetically by roughly 100,000 polymorphic sites, providing for near infinite variety. As only a small fraction of these single nucleotide polymorphisms will prove relevant to drug response, our goal will be to identify the most important variants.

Microarray gene chips

Novel technology in the form of microarray chips enables us to scan the entire human genome for relevant polymorphisms.[12,13] We can determine simultaneously many thousands of polymorphisms in a patient. At present, these single nucleotide polymorphisms are selected merely as markers evenly distributed throughout the genome, in the hope that functionally relevant polymorphisms can be associated with specific markers by virtue of their proximity on the chromosome. Such genome-wide association studies are already being used in the discovery of susceptibility genes for diseases such as asthma and prostrate cancer, but they are equally suitable for determining the genes involved in drug response. Genome-wide scanning can identify these genes even if we do not know the mechanisms by which the drug acts in the body. The French genomics company, Genset, currently uses gene chips with 60,000 single nucleotide polymorphism markers—sufficient for a complete genomic scan—applied to clinical drug trials in partnership with major pharmaceutical companies. Expanding the number of single nucleotide polymorphisms and selecting functionally relevant single nucleotide polymorphisms in coding or promoter/enhancer regions of genes is quite feasible with current technology and would greatly enhance the power of genome-wide scanning. Herein lies the main incentive for the current rush in the pharmaceutical industry to patent single nucleotide polymorphism markers. It might also be possible to salvage useful experimental drugs that would have failed with standard clinical trials, because of an unacceptable incidence of toxicity in a poorly defined patient population. Stratifying patient populations in relation to genetic criteria emerges as a major challenge to the pharmaceutical industry. Undoubtedly, the insights expected to emerge from such an approach are staggering, but they cannot be gauged accurately at present.

Chip technology

Microarrays can further serve to determine the expression pattern of genes in a target tissue. This shows the mechanisms of drug action in a genomic context. It can also clarify interindividual differences in drug response that are downstream of immediate drug effects in the body by shear force of the massive amount of information emanating from chip technology. Analyzing the entire transcriptional program of a tissue, for example fibroblasts in response to serum stimulation,[14] provides unprecedented details of a complex system and leads to new insights in pathophysiology and biological drug response. Tissue transcript profiling is especially appropriate in cancers because mRNA can be extracted from biopsy specimens or surgical samples. Altered gene expression in the tumor can serve as a guide for selecting effective drug therapy or avoiding unnecessary exposure to toxic but ineffective drugs—for example the overexpression of drug resistance genes encoding transporters (Table 1).

PROMISE OF PHARMACOGENOMICS

These advances are the harbinger of profound changes in treatment. What then do we expect to gain from pharmacogenomics? In the near future, genotyping can help avert severe drug toxicity that is genetically determined but occurs only rarely. Alternatively, drugs may be designed a priori so that they are not subject to extreme variations that result from a few well defined polymorphisms. Drug structures under development are already being selected so that they do not interact with cytochrome P-450 subtype CYP2D6 to avoid unwarranted toxicity in people who metabolize this poorly.

Predicting drug efficacy

Looking farther ahead, and on a much broader scale, we could improve drug efficacy by distinguishing between people who respond well to a drug and those who respond poorly. Often, an effective drug response is found in a few patients treated, while most benefit little or not at all. Much could be gained if we could select the optimal drug for the individual patient before treatment begins. Perhaps a gene chip that establishes a single nucleotide polymorphism signature involving multiple genes relevant to therapeutic outcome for each individual will be developed. This signature could offer insights into an individual's susceptibility to disease and responsiveness to drugs, enabling optimal drug selection by genetic criteria. For example, cure rates with combined surgical and drug treatment of advanced colorectal carcinoma range from 20% to 40%, while the remainder of the patients experience little gain or even severe toxicity from chemotherapy. If we could predict which patients respond best to a particular drug—or better, which drug will yield optimal effects for a given patient—much will be gained. The success of this approach will depend critically on the selection of single nucleotide polymorphisms tested by the gene chip. Single nucleotide polymorphisms must be informative and many must be tested to scan the entire genome. This task is by

no means complete and constitutes a major goal of those companies which are focusing on genomics.

LIMITATIONS

There are also formidable obstacles that we are unlikely to overcome in the near future. The dynamic complexity of the human genome, involvement of multiple genes in drug responses, and racial differences in the prevalence of gene variants impede effective genome-wide scanning and progress towards practical clinical applications. Furthermore, the drug response is probably affected by multiple genes, each gene with multiple polymorphisms distributed in the general population. For example, the anticancer drug 5-fluorouracil used in the treatment of colorectal cancer is activated and inactivated by nearly 40 different enzymes. Each of these is currently being scanned for relevant polymorphisms at the biotech company Variagenics. Dihydropyrimidine dehydrogenase is a likely candidate in 5-fluorouracil inactivation (Table 1). However, whether extensive genotyping will provide useful predictors of clinical response remains to be seen.

Racial differences add further confounding factors. Drug response might be predicted from a certain pattern of polymorphisms rather than only a single polymorphism, yet these patterns probably differ between ethnic groups. This could prevent us from making predictions about drug responses across the general patient population, and it emphasizes the need to stratify clinical pharmacogenomic studies.

Genomic technologies are still evolving rapidly, at an exponential pace similar to the development of computer technology over the past 20 years. We are not certain where genomic technologies will be 10 years from now.

Ethical issues also need to be resolved. Holding sensitive information on someone's genetic make up raises questions of privacy and security and ethical dilemmas in disease prognosis and treatment choices. After all, polymorphisms relevant to drug response may overlap with disease susceptibility, and divulging such information could jeopardize an individual. On the other hand, legal issues may force the inclusion of pharmacogenomics into clinical practice. Once the genetic component of a severe adverse drug effect is documented, doctors may be obliged to order the genetic test to avoid malpractice litigation.

IMPACT OF PHARMACOGENOMICS

Pharmacogenomics will have profound impact on the way drug treatment is conducted. We can include here bioengineered proteins as drugs, or even gene therapy designed to deliver proteins to target tissues. These treatments are also subject to constraints and complexities engendered by individual variability. A case in point is the treatment of breast cancer with trastuzumab (Herceptin; Genentech, USA) a humanized monoclonal antibody against the HER2 receptor. Overexpression of HER2 may occur as a somatic genetic change in breast cancer and other tumors. This correlates with poor clinical prognosis and serves as a marker for effective therapy with trastuzumab, either alone or in combination with chemotherapy.[15,16]

Whether we will see broad use of gene chips in clinical use within 10 years is questionable, but the mere knowledge of the principles underlying genetic variability will prove valuable in optimizing drug therapy. Pharmacogenomics will lead us towards individualized therapy, but it will also help us understand limitations inherent in treating disease in a broad patient population

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Xenotransplantation: progress and promise

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Extensive research in xenotransplantation is being propelled by the critical shortage of allotransplants. About a third of the patients on organ waiting lists in the United States die for lack of available organs, and in the United Kingdom fewer than 30% of those waiting for kidneys receive them each year.[1-3] The human toll of suffering in patients who need transplants is great, and their quality of life is poor.

This update focuses on whole organ xenotransplants. It draws on the latest published studies and the assessments at two recent meetings—a conference of US and UK scientists, ethicists, and policy experts in New York in May 1999, and the June 1999 meeting of the xenotransplantation subcommittee of the US Food and Drug Administration's Center for Biologics Evaluation and Research.

Research is currently being conducted in all the critical areas of xenotransplantation, and this will, it is hoped, make xenotransplants safe and effective for human beings. These critical areas include immunological barriers, physiological functioning, infectious disease risks, and pivotal ethical issues.

IMMUNOLOGICAL BARRIERS

Over time, xenotransplantation has proved to be daunting because of organ rejection. Rejection occurs in several stages: hyperacute rejection, acute vascular rejection, cellular rejection, and chronic rejection.[2-4] Hyperacute rejection and acute vascular rejection are mediated by antibodies against oligosaccharide determinants on pig vascular endothelium.[5] These forms of rejection occur rarely with human allografts, which are associated more with cellular and chronic rejection.

Hyperacute rejection

Hyperacute rejection is now being overcome. While several approaches are possible, the most successful currently involves producing transgenic pigs that express human complement regulatory proteins capable of inhibiting the injurious effect of antibody mediated complement activation on the vascularized pig organ.[6,7] One biotechnology company, for example, has transplanted transgenic pig organs into non-human primates and has achieved a hyperacute rejection rate of less than 2%.

Acute vascular rejection

Part of the problem in overcoming acute vascular rejection is the fact that the biology of this form of rejection is incompletely understood. Reports from two biotechnology firms presented at the June meeting of the xenotransplantation committee of the Food and Drug Administration Center for Biologics Evaluation and Research indicated that the organ survival times of transgenic pig hearts and kidneys in non-human primates (hereafter referred to as primates) varied from a few days to several weeks. Effective immunosuppresive regimens for primates are in development, and some of the regimens now used could not be tolerated by humans. Researchers cannot yet control acute vascular rejection. However, progress is being made on several fronts, including the development of new immunosuppressive drugs and further attempts to genetic engineer pigs.

Cellular rejection

Although the strength of cellular rejection in xenografts remains uncertain, it is expected to be stronger than that seen in allografts. It is also anticipated that chronic rejection (for example, graft arteriosclerosis) of xenotransplants will be more aggressive than in allografts. Overcoming these barriers will probably require severe and sustained concentrations of immunosuppressive drugs or breakthroughs in the development of human immunological tolerance to porcine organs.[8]

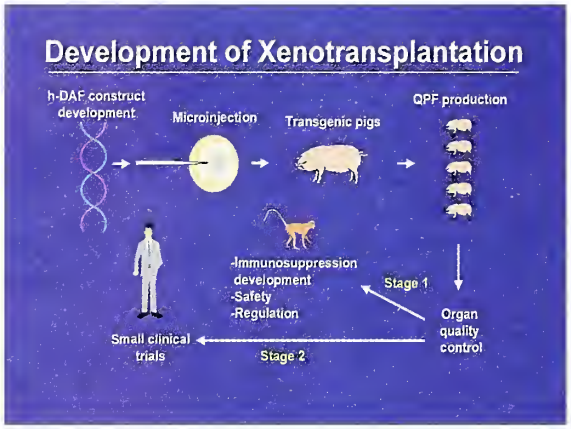
PHYSIOLOGICAL FUNCTIONING

Extensive research will be needed to determine whether animals organs can replace the physiological functions of human organs—research is being carried out in fields such as anatomical design, metabolism, hormonal function, and blood viscosity and coagulation.[9] One biotechnology company reported to the Food and Drug Administration meeting that pig to primate kidney transplants function well on several levels, but lack compatibility in respect of erythropoietin function.

Researchers now predict that pig to human transplants of hearts, kidneys, and lungs will be physiologically feasible. However, this is not the case for whole organ liver transplants, where differences between many of the proteins manufactured in the liver may prohibit adequate function. Lung transplants will also require far more research into physiology and risks of infectious disease.

Summary points

- Xenotransplantation research is driven by the acute shortage of available allotransplants
- Although one longstanding problem, hyperacute rejection of xenotransplants, is being overcome, daunting immunological barriers remain
- Great attention must be given to the physiological functions of porcine organs in human beings
- Worries over the infectious disease potential of porcine xenotransplants are easing
- Ethical concerns over xenotransplants, including the challenge of identifying patients who might be approached as subjects of reinitiated clinical trials, are being explored



RISKS OF INFECTIOUS DISEASE

The infectious disease risks of xenotransplants pose a problem for the recipients of organ transplants and the public at large. The public health risk that xenotransplantation might created a new infectious disease epidemic represents a major ethical concern that is the subject of widespread discussion and controversy.[10,11]

Two years ago, the risk that pig to human transplants might spread infectious disease was regarded as so worrisome that the Food and Drug Administration placed a hold on ongoing clinical trials involving new drug developments and cellular xenotransplants—porcine islet cells, hepatocytes, and so on. The hold was to continue until the companies sponsoring these trials developed assays that could detect and identify potential porcine endogenous retroviruses that had just been shown to infect human cells in vitro.[12-14] Because endogenous retroviruses are found in the DNA of all mammalian species, they cannot be "bred out" of xenotransplants. In contrast, the many other infectious diseases of pigs can be excluded by breeding and safety measures that produce pathogen free colonies.[15]

Several developments since October 1997 support the conclusion that there is no appreciable current evidence of porcine endogenous retrovirus infection in human recipients of xenotransplants.[16,17] Although most of the human recipients were exposed to porcine tissue for relatively brief periods of time, evidence from independent researchers and several sponsors of trials now indicates that porcine endogenous retrovirus infectivity is either non-existent or confined to very low levels that probably result from the presence of retrovirus in source cells. These reassuring findings led the Food and Drug Administration to conclude that six of the 10 sponsors of clinical trials involving xenotransplant cells had addressed adequately the safety concerns identified in 1997.

With regard to public health risks, evidence on porcine endogenous retrovirus infectivity in human cells in vitro[11,12] and the creation and onset of the HIV virus[18] led the Food and Drug Administration to decide in April 1999 that protocols involving primate xenografts in humans should not be submitted until their risks are known, addressed, and discussed publicly.[19] This accords with a conclusion in the report from the UK Advisory Group on the Ethics of Xenotransplantation that primates should not be used as source animals for humans.[20]

The infectious disease risks posed by porcine endogenous retrovirus is a topic of continued concern and discussion. Even though the Food and Drug Administration knew that sensitive tests for porcine endogenous retrovirus have recently been developed, its xenotransplant subcommittee called last June for greater standardization and quality control of infectious diseases assays, new assays to test viral expression in plasma, and other yardstick safety measures that should be developed and refined.

ETHICAL ISSUES

Although the infectious disease risks of xenotransplants is a major ethical concern, all of the topics discussed above pertain to ethics because they are pivotal to an analysis of the risks and benefits of clinical trials. These scientific ethical issues pertain to the first required level of ethical analysis of clinical research, which is discussed under the rubric of "beneficence" in the 1979 "Belmont report" of the US National Commission,[21] and is addressed in the regulations of respective nations and in official reports on the ethics of xenotransplantation from the United States and the United Kingdom.[1,20]

Additional ethical issues include the use of animals, genetic alterations of animal species, the complexities of informed consent for research subjects, the justice of including or excluding respective groups of human subjects in clinical trials, and the imperative of educating the public lest it feel that researchers and biotechnology firms are forging ahead without public awareness.[1,11,20,22,23]

A critical and neglected ethical issue involves identifying the populations of patients who might become the early subjects of reinitiated clinical trials.[22-24] The UK Kennedy report recommends that children and others incapable of giving informed and legally valid consent should be excluded until "initial concerns about safety and efficacy have been satisfactorily resolved."[20] But how will these initial concerns be resolved?

This topic was discussed at length at the June meeting of the xenotransplantation committee of the Food and Drug Administration Center for Biologics Evaluation and Research. Viewed as initial and far from definitive, the discussion first focused on what kinds of preclinical data are necessary to assure benchmark levels of success and safety in human trials. The subcommittee agreed that, given our greater knowledge of human immunological suppression and infection control, the success of human trials is likely to be greater than the present pig to primate transplants. Yet most members of the subcommittee be-

lieved that human trials should not be allowed until preclinical studies show more success. Most recommended that before human trials resume, the success rate of pig to primate transplants should be raised from the present 50% organ survival rate for less than 1 month to a 90% survival rate for 2 months, and a 50% rate for 3 months.

Discussion then turned to populations of patients who might stand to benefit from clinical trials. Xenotransplants as bridges to allotransplants might improve the survival chances and quality of life of some patients. And xenotransplants could serve as definitive transplant treatment for some groups of patients who are excluded from allotransplant waiting lists. Several groups were identified and discussed under the proviso that preclinical data do not yet warrant a renewal of clinical trials. Starting these trials too early could bring more harm than benefit to patients and adversely affect public opinion and current and future progress.

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What is immoral about eugenics?

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It is a given in discussions of genetic engineering that no sensible person can be in favor of eugenics. The main reason for this presumption is that so much horror, misery, and mayhem has been carried out in the name of eugenics in the 20th century that no person with any moral sense could think otherwise.[1-3] In fact, the abysmal history of murder and sterilization undertaken in the name of race hygiene and the "improvement" of the human species again and again in this century is so overpowering that the risk of reoccurrence, sliding down what has proved time and time again to be an extremely slick, slippery slope, does seem enough to bring all ethical argument in favor of eugenics to an end.

However, before dismissing any favorable stance toward eugenics, it is important to distinguish what has happened in the past under the banner of eugenics and what might happen in the future. It is important to distinguish between genetic changes undertaken with respect to improving a group or population and genetic change that takes a single individual as its focus.

Efforts to change the genetic makeup of a group or population almost always require third parties to be involved in the personal reproductive choices of individuals and couples. Someone besides the individuals making children has to set a policy and a standard. In our century, these efforts have almost always incorporated force or coercion since individuals may not agree with the policy or third parties may seek to force their vision of improvement on an unwilling population.

It is, however, a different matter for couples to undertake their own efforts to use genetic technologies and knowledge to improve the potential of their offspring.

Summary points

- The horrible abuses committed in the name of eugenics through coercive policies imposed by governments have obscured the fact that eugenic goals can be the subject of choice as well as coercion
- In the rush to map the human genome and reap the benefits of new genetic knowledge, it has become commonplace to argue that eugenic goals will play no role in how new genetic knowledge is used
- The moral case against voluntary choices to advance eugenic goals by individuals or couples has not been persuasively made
- Given the power and authority granted to parents to seek to improve or better their children by environmental interventions at least some forms of genetic selection or alteration seem equally ethically defensible if they are undertaken freely and do not disempower or disadvantage children

Eugenics has not, until the advent of genetic engineering, offered this option. Efforts to change the inherited genetic makeup of a particular person may be the result of third party involvement, but it is far more likely that such efforts will be the result of individual reproductive choice.[4] To put the point another way, population eugenics involves commanding people to produce desired genotypic or phenotypic traits. This sort of eugenics is not the same as allowing an individual or couple voluntarily to choose a heritable trait in their sperm, egg, embryo, or fetus, motivated by their view of what is good or desirable.

The most common arguments against any attempt to either avoid a trait through germline genetic engineering or to create more children with desired traits fall into three categories: worries about the presence of force or compulsion, the imposition of arbitrary standards of perfection,[4] or inequities that might arise from allowing the practice of eugenic choice.[5] The first worry is not one that seems insurmountable as an objection to allowing individual choice about germline changes. The latter two may also not discount eugenic choices.

COERCION

Certainly it is morally objectionable for governments or institutions or any third party to compel or coerce anyone's reproductive behavior.[1,3] The right to reproduce without interference from third parties is one of the fundamental freedoms recognized by international law and moral theories from a host of ethical traditions. However, the goals of obtaining perfection, avoiding disease, or pursuing health with respect to individuals need not involve coercion or force.

A couple may wish to have a baby who has no risk of inheriting Tay-Sachs disease or transmitting sickle cell disease. Or they may want a child with a particular hair color or gender. If their choice is free and informed then there is no reason to think that such a choice is immoral on grounds of force or coercion.

THE SUBJECTIVITY OF PERFECTION

Some who find the pursuit of perfection morally objectionable worry about more than coercion. They note that it is simply not clear which traits or attributes are properly perceived as perfect or optimal. The decision about what trait or behavior is good or healthy depends on the environment, culture, and circumstances that a child will face. Stigma and prejudice need not be the inevitable result of choice.

Views about what is perfect or desirable in a human being are, more often than not, matters of taste, culture, and personal experience. But they are not always simply the product of subjective feelings. There are certain traits—physical stamina, strength, speed, mathematical ability, dexterity, and acuity of vision, to name only a few—that are related to health in ways that command universal assent as to their desirability. It would be hard to argue that a parent who wanted a child with better memory or greater physical dexterity was simply indulging his or her biases or prejudices. As long as people are not forced to make choices about their children that are in conformity with particular visions of what is good or bad, healthy or unhealthy, there would seem to be enough consensus about the desirability of some traits to permit parents to make individual choices about the traits of their children in the name of their health. And if no coercion of compulsion were involved it could even be argued that parents should be free to pick the eyebrow shape or freckle pattern of their children or other equally innocuous traits as long as their selection imposed no risk for the child, did not compromise the child's chance of maximizing his or

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All parents want good and healthy traits in their children

her opportunities, or lead to parents becoming overly invested in superficial aspects of the child's appearance or behavior.[4,6]

A parent might concede that their vision of perfection is to some degree subjective but still insist on the right to pursue it. Because we accept this point of view with respect to child rearing, allowing parents to teach their children religious values, hobbies, and customs as they see fit, it would be difficult to reject it as overly subjective when matters turn to the selection of a genetic endowment for their child.

For many years cosmetic surgeons, psychoanalysts, and sports medicine specialists have been plying their trades without all people with big noses or poor posture feeling they need to visit specialists to have these traits altered. Some people choose to avail themselves of these specialists in the pursuit of perfection. Many do not. If there is a slope from permitting individual choice of one's child's traits to limiting the choices available to parents it is a slope that does not start with individual choice. And if there is a problem of a slope then it must be shown why it is morally permissible for parents to seek betterment after a child is born but why such efforts are wrong if genetic alteration is used. There is nothing terrible about subjectivity in a decision to indulge preferences about the traits of one's child as long as those preferences do nothing to hurt or impair the child.

EQUALITY

Another objection to allowing eugenic desires to influence parenting is that this will lead to fundamental social inequalities.[5] Allowing parental choice about the genetic makeup of their children may lead to the creation of a genetic "overclass" with unfair advantages over those who parents did not or could not afford to endow them with the right biological dispositions and traits. Or it may lead to homogenization in society where diversity and difference disappear in a rush to produce only perfect people, leaving anyone with the slightest disability or deficiency at a distinct disadvantage. Equity and fairness are certainly important concepts in societies that are committed to the equality of opportunity for all. However, a belief that everyone deserves a fair chance may mean that society must do what it can to insure that the means to implementing eugenic choices are available to all who desire them. It may also mean that a strong obligation exists to try and compensate for any differences in biological endowment with special programs and educational opportunities. It is hard to argue in a world that currently tolerates so much inequity in the circumstances under which children are brought into being that there is something more offensive or more morally problematic about biological advantages as opposed to social and economic advantages.

It is difficult to argue in a world that tolerates the creation of homogeneity through the parental selection of schools, music lessons, religious training, or summer camps that only environmentally engineered homogeneity is morally licit. The fact that those people with privileged social backgrounds go on to similar sorts of educational and life experiences does not seem sufficient reason to interfere with parental choice.

No moral principle seems to provide sufficient reason to condemn individual eugenic goals. While force and coercion, compulsion and threat have no place in procreative choice, and while individual decisions can have negative collective consequences, it is not clear that it is any less ethical to allow parents to pick the eye color of their child or to try and create a fetus with a propensity for mathematics than it is to permit them to teach their children the values of a particular religion, try to inculcate a love of sports by taking them to football games, or to require them to play the piano. In so far as coercion and force are absent and individual choice is allowed to hold sway, then presuming fairness in the access to the means of enhancing our offsprings' lives it is hard to see what exactly is wrong with parents choosing to use genetic knowledge to improve the health and wellbeing of their offspring.

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capsule

High—tech hernias Most hernias are still diagnosed accurately using clinical means but a review in the *British Journal of Surgery* (1999;86:1243-1250) suggests that cross sectional imaging may have a role in some cases. The increasing quality of both computed tomography and magnetic resonance imaging over the past decade provides increasingly accurate assessment of the neck of the sac and its contents, enhancing diagnostic accuracy in obese patients with intestinal obstruction, and occasionally avoiding the need for surgery.

Detecting coronary calcification with electron beam computed tomography: its role in managing coronary artery disease

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Electron beam computed tomography is a sensitive technique that detects and quantifies the extent of coronary atherosclerosis by imaging coronary calcification. In comparison with other techniques such as angiography, electron beam computed tomography can detect both early and advanced coronary atherosclerosis.

METHODS

The literature for this review was identified using the MEDLINE database (1966-1999) and bibliographies of existing literature.

CASE PRESENTATION

A 59-year-old white man was referred for cardiovascular screening prior to starting an exercise program. He had no history of coronary artery disease or cardiovascular symptoms, took no medications regularly, and was a non-smoker. Past medical history was notable for borderline hypertension, and an abnormal lipid panel. His physical examination was notable for a blood pressure of 135/89 mm Hg. Laboratory testing revealed a fasting serum cholesterol level of 179, low density lipoprotein (LDL) cholesterol level of 83, and high density lipoprotein (HDL) cholesterol level of 21. A 12-lead electrocardiogram was normal.Electron beam computed tomography was recommended because of his cardiovascular risk factors. This study showed extensive calcifications in the right coronary artery, left anterior descending artery and a total calcium score (Agatston method) of 1101 (Figure 1). An exercise test with myocardial perfusion imaging was performed, during which the patient exercised to 15 minutes on a Bruce protocol. The perfusion images were normal. When further serologic studies were conducted, including lipoprotein (a) and small dense low density lipoprotein levels, results were within normal limits. An exception was the fasting serum homocysteine level, which was 15.2 ng/dL (abnormally high). The patient began a daily therapeutic regimen of 325 mg aspirin, 1 mg folate (for homocysteine reduction), 50 mg atenolol (for hypertension), and 40 mg pravastatin (to improve the LDL/HDL ratio). One year later, the patient's serum high density lipoprotein level had improved to 32 mg/dL, his blood pressure was 125/80 mm Hg, and he was asymptomatic during regular aerobic exercise.

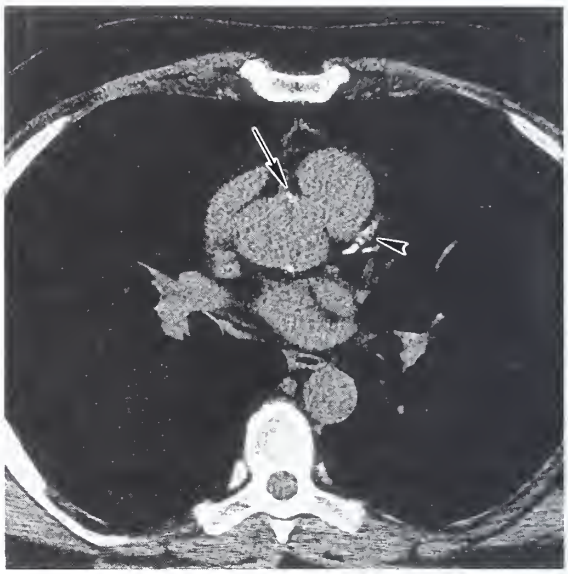

Figure 1 Electron beam computed tomographic scan showing calcification in the mid-portion of the left anterior descending coronary artery (arrowhead) and ostium of the right coronary artery (arrow)

Summary points

- Electron beam computed tomography accurately quantifies the presence and extent of coronary calcification.
- Coronary calcification always indicates the presence of atheromatous plaque. The prevalence of coronary calcification increases with age and is related to underlying cardiovascular risk factors.
- Coronary calcification identifies patients at an increased risk of cardiovascular events.
- Patients with coronary calcification should be considered for aggressive risk factor modification and preventive treatments such as beta blockers for silent ischemia, aspirin and drugs to lower cholesterol.

DISCUSSION

Electron beam computed tomography and coronary artery disease

Electron beam computed tomography produces electrocardiographically gated still-frame images of the heart, which are used to quantify the presence and extent of coronary calcification. The test is noninvasive, rapid, and costs between $400 and $500. There are only between 50 and 100 of these scanners in the United States; however, other types of computed tomography scanners (such as spiral computed tomography) may provide a reasonable alternative for coronary calcium detection. Based on the detection of discrete coronary calcifications in the epicardial coronary vessels, a calcium scoring system has been

developed and validated with pathologic studies by Agatston and colleagues.[1] The calcium score is a unitless measurement calculated as the product of the area of calcification (in mm^2) and the density score (each segment of detected calcium is rated on a scale from 1 to 4 based on the maximal computed tomography density in Hounsfield units). Typically, results from electron beam computed tomography are reported as a composite calcium score for the entire epicardial coronary system (range 0 - >1000). Any score above zero indicates the presence of coronary calcification.

Coronary calcification is always associated with atheromatous plaque. The prevalence of coronary calcification increases with age.[2] Calcium scores hold similar significance in men and women,[3] although for any given score, women tend to be approximately a decade older than men.[2] Coronary calcification is related to conventional coronary risk factors, although these risk factors explain only 40% of the variability of coronary calcification.[4]

Clinical uses

Asymptomatic populations

Acute ischemic coronary events arise most commonly from plaque rupture or erosion of mild, nonobstructive arterial stenoses. Plaque characteristics unrelated to the degree of stenosis, such as lipid content and thickness of the plaque fibrous cap, are better predictors of rupture than is the degree of obstruction.[5] Assuming that calcification is a sensitive marker for all atheromatous disease, regardless of the degree of obstruction, electron beam computed tomography can provide earlier detection of subclinical disease.

Preliminary evidence suggests that it may be a useful aid to predicting which asymptomatic patients are at risk for cardiovascular events.[6] But, whether coronary calcium is a better marker of cardiovascular risk than traditional risk factors is controversial. Nonetheless, because silent myocardial ischemia is an important predictor of prognosis, patients with a calcium score of 400 should be referred for stress imaging procedures.[7] Almost 50% of such patients will have abnormalities on myocardial perfusion studies, indicating the presence of myocardial ischemia. In most cases, these patients would be appropriate candidates for medications to suppress ischemia, for example with beta blockers,[8] to improve prognosis. An electron beam computed tomographic scan that yields no or few findings does not confer the complete absence of risk for cardiovascular events.[9]

We recommend limiting screening to men over the age of 40, and women over the age of 50, because of the low prevalence of calcification in younger men and women. Patients who are referred should have modifiable coronary risk factors, to optimize the therapeutic impact of the test.

Symptomatic patients

The presence and extent of coronary calcification is related to the severity coronary artery disease on angiography. Electron beam computed tomography has a sensitivity of 81% to 94% and a specificity of 72% to 86% for the diagnosis of any angiographic coronary artery disease.[10] For obstructive coronary artery disease (>50% stenosis of any epicardial vessel), the sensitivity and specificity are approximately 95% and 50%, respectively.[10,11] Thus, electron beam computed tomography may be used to rule out obstructive coronary artery disease in patients with atypical symptoms and a low to intermediate pre-test probability. A value of 123 for the coronary calcium score has been proposed as a cutoff at which the sensitivity and specificity for detection of a 70% stenosis is 82%.[11,12] False-negative studies may be more common in young patients due to the presence of early, noncalcified atherosclerosis.[13] The higher the calcium score, the greater the likelihood of obstructive coronary artery disease.[12] The accuracy of exercise testing, myocardial perfusion imaging, and electron beam computed tomography for the identification of patients with obstructive coronary artery disease are comparable.[14] But, because the inter-test agreement of these tests is limited, these methods are best considered complementary.

Potential impact on patients and physicians

Patients with traditional risk factors for cardiac disease should be treated using accepted efficacy endpoints (such as the National Cholesterol Education Program guidelines), regardless of the results of electron beam computed tomographic assessment. For patients with borderline risk factors, however, the finding of coronary calcification using this test may justify a more intensive approach to risk factor modification than is indicated by these guidelines.[15] Preliminary evidence suggests that an abnormal result from electron beam computed tomographic testing may create a teachable moment for patients.[15] For example, evidence of early atherosclerosis on electron beam computed tomographic scans could be used to motivate a smoker to stop smoking. While more evidence is needed,[16] it may become an important tool for targeting interventions and improving adherence to treatment recommendations in preventive cardiology.

Use for screening for cardiovascular disease

Overall, positive and negative results of electron beam computed tomography must be interpreted in light of the patient's age, and with the understanding that the implications of the test are probabilistic (Figure 2). Patients with no detectable calcification can generally be reassured that the test suggests a low probability of severe atherosclerosis and a low short-term (several years) risk of cardiovascular events. False-negative test results can occur,

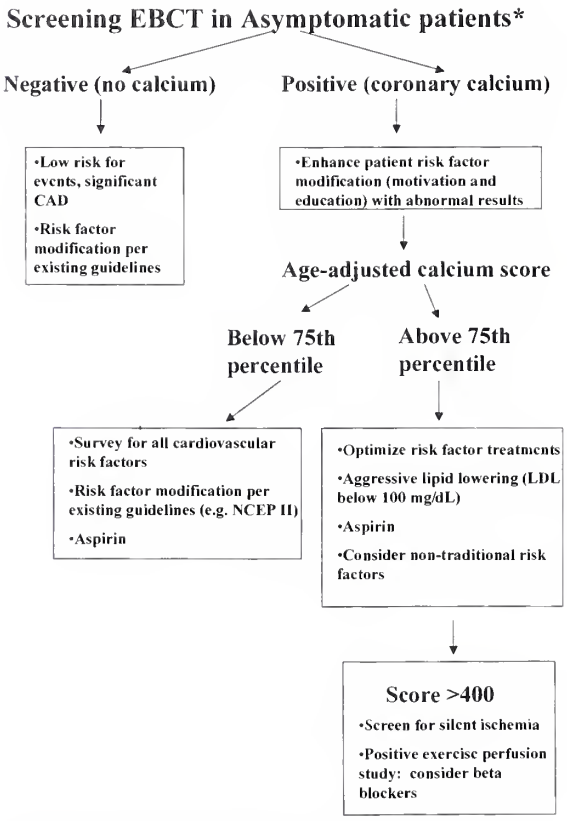

Figure 2 Flow diagram showing interaction between electron beam computed tomography results and clinical management.
Screening electron beam computed tomography population:

- Asymptomatic for coronary artery disease
- Age: men ≥40; women ≥50
- 1 or more cardiovascular risk factors

however. Thus, with a patient who has a high probability of coronary artery disease prior to the test, less confident statements about the nature of the results, and perhaps additional testing (for example, myocardial perfusion imaging) may be worth considering. In patients 40 years of age or younger, coronary calcification is less common, thus the diagnostic utility of a negative result is limited. For patients with negative findings, the strategies for risk factor modification should follow conventional guidelines for primary prevention.

Patients in whom scanning shows coronary calcification will often be anxious about the results. Counseling can be time consuming as patients must be educated about the atherosclerotic process and their coronary risk factors. The age of the patient is critical to determining how to counsel a patient about their risk of developing clinical manifestations of cardiovascular disease. Sedentary patients should undergo exercise stress testing prior to starting exercise programs. Patients with abnormal results of scans should be carefully examined for modifiable coronary risk factors. From the physician's perspective, the finding of any coronary calcification in a young patient or excessive (upper quartile relative to the patient's age) calcification may alter the medical approach to coronary risk. Considerations include prescribing aspirin and perhaps applying a lower threshold for initiating the use of drugs to lower cholesterol levels. For patients with few modifiable risk factors, further consideration of non-traditional risk factors (for example, homocysteine) or therapies (vitamin E) may be warranted.

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COMMENTARY:
How much will it cost?

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Taylor and O'Malley present a strategy for the use of a new technology, electron-beam computed tomography, in the evaluation of possible coronary artery disease in asymptomatic individuals. Although their recommendations are generally consistent with others in the literature, readers should approach them with caution, and ask. They should not only ask those questions that are appropriate to all screening tests, but particularly those that are applicable to new technologies, especially ones that are expensive, highly marketed and potentially enormously profitable, technologies.

The authors' observation that "presence of calcium always implies presence of plaque" may be true in the pathology lab, but it is not true if the calcium "detected" by electron-beam computed tomography isn't really there (ie, the test is falsely positive). If the specificity of the test were as high as 95%, that would mean that 1 in 20 healthy people without any calcium whatsoever would be told (wrongly) that their coronary arteries contain plaque. Furthermore, although "the presence of plaque" sounds ominous, it often has no clinical significance. Although higher calcium scores (and more plaque) predict some increased likelihood of coronary artery disease in populations, most people with some calcium (and plaque) in their arteries never have coronary artery disease.

This leads to the far greater problem of tests that are falsely positive for clinically significant lesions, always a concern with screening tests, as by definition they are almost always done in populations without a high prevalence of disease. Although many 50-year-olds are walking around with calcium in their coronaries, most of them don't have coronary artery disease. Since the test itself is only moderately accurate, most of the "positives" turn out actually to be falsely positive. The authors describe this test as "non-invasive," but it will surely lead to subsequent invasive testing (such as angiography) and considerable anxiety in many normal individuals.

The authors suggest that the fear engendered by coronary artery disease can result in a "teachable moment," in which patients can be persuaded to get serious, finally, about such things as lifestyle and risk-factor modification. This may be true, although an only moderately accurate test, that measures only a surrogate marker for disease, might not be the best tool to use to encourage patients to do the right thing. More importantly, the authors don't consider the possibility of an "obfuscating" moment, that is just as likely to occur due to a false negative test. What about patients who figure they don't need to quit smoking, because "you just told me yourself, doc, that my coronary arteries are clean!"?

Whenever a new technology is unveiled, it is easy to highlight its potential for good. But when new ideas finally undergo real testing—not about how they measure some parameter, or imaging some vessels, or identify cancer, but seeing if about whether they improve outcome—many prove far less beneficial, and/or are associated with adverse consequences. Taylor and O'Malley's strategy might identify early coronary artery disease in some asymptomatic patients, and lead to earlier medical or surgical interventions, each of which could possibly end up saving lives. It might also cause unnecessary worry, "medicalize" healthy individuals into "patients," and affect their insurability. It could consume an enormous amount of the already limited doctor-patient communication time, when patients want to know what to do about the results. It could lead to unnecessary interventions, with adverse medical effect, or unwittingly convince some patients to abandon necessary therapy, even while (perhaps) failing to benefit most people who access it. It probably does a little of each of all these things, and it would be nice to know which, and to what degree, before we all started to use it. Taylor and O'Malley are apparently now studying this very question, at present,[1] but without any completed research that to date addresses the impact on real patient outcomes, I remain skeptical.[1]

This is especially true given that much of the impetus behind electron-beam computed tomography is economically driven, as Taylor and O'Malley point out in their own, more critical editorial in the New England Journal of Medicine, December, 1998.[2] They noted that most of the relatively few scanners available in the US are owned by for-profit companies, who are aggressively marketing directly to consumers, and accepting self-referrals from patients. This is hardly surprising, given the staggering profits (and costs) that would result from doing this test in the hundreds of millions of "appropriate" candidates. Nor is it surprising that many more machines are on their way. Even if some people will benefit from these tests, who will pay for them, and for follow-up tests and interventions? Shouldn't we have some idea about the value we're getting for all that money, before we decide to buy electron-beam computed tomography screening tests for our patients?

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CLINICAL EVIDENCE

Psychosocial factors in the etiology and prognosis of coronary heart disease: systematic review of prospective cohort studies

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Do psychosocial factors cause coronary heart disease or affect survival among patients with coronary heart disease? Here we use an explicit methodological quality filter to review systematically prospective cohort studies that test specific psychosocial hypotheses. This review of the epidemiological literature identifies the psychosocial factors that have been most rigorously tested. Only four psychosocial factors met the quality filter: type A/hostility, depression and anxiety, work characteristics, and social supports. The importance of other study designs (for example, ecological[1] or nested case-control[2-4] studies) is acknowledged. The review should be seen as complementary to existing reviews[5-8] on single psychosocial factors and as a challenge to investigators in the field to ensure that the systematic review is made unbiased, kept up-to-date, and used to guide future hypothesis testing.

WHAT IS A PSYCHOSOCIAL FACTOR?

A psychosocial factor may be defined as a measurement that potentially relates psychological phenomena to the social environment and to pathophysiologic changes. The validity and reliability (precision) of the questionnaire-based instruments used to measure psychosocial factors have been improved through the use of psychometric techniques. By avoiding the unhelpful general term of "stress," recent work has developed theoretical models (for example, the job control-demands-support model of psychosocial work characteristics) which generate specific hypotheses that can be tested.

Summary points

- In healthy populations, prospective cohort studies show a possible etiological role for type A/hostility (6/14 studies), depression and anxiety (11/11 studies), psychosocial work characteristics (6/10 studies), and social support (5/8 studies)
- In populations of patients with coronary heart disease, prospective studies show a prognostic role for depression and anxiety (6/6 studies), psychosocial work characteristics (1/2 studies), and social support (9/10 studies); 0 of 5 studies showed a prognostic role for type A/hostility
- Although this review cannot discount the possibility of publication bias, prospective cohort studies provide strong evidence that psychosocial factors, particularly depression and social support, are independent etiological and prognostic factors for coronary heart disease

HOW MIGHT PSYCHOSOCIAL FACTORS BE LINKED TO CORONARY HEART DISEASE?

Evidence of mechanisms linking psychosocial factors with coronary heart disease (reviewed elsewhere[9,10]) is important in making causal inferences and, therefore, in designing preventive interventions. Psychosocial factors may act alone or combine in clusters[11] and may exert effects at different stages of life.[12] Broadly, three interrelated pathways may be considered. First, psychosocial factors may affect health-related behaviors such as smoking, diet, alcohol consumption, or physical activity that in turn may influence the risk of coronary heart disease.[13] If such behaviors lie on the causal pathway between psychosocial factors and coronary heart disease, then treating them as confounding variables, as some studies do, must be questioned. Second, psychosocial factors may cause direct acute or chronic pathophysiologic changes. Third, access to and the content of medical care may plausibly be influenced by, for example, social supports (but there is little direct evidence for this). Although it is beyond the scope of this review to consider the determinants of adverse psychosocial factors, socioeconomic status is inversely associated with coronary heart disease[14] and also with certain psychosocial factors, and it has been proposed that psychosocial pathways may play a mediating role.[15,16]

METHOD OF SYSTEMATIC REVIEW

A methodologic quality filter was used to select studies for inclusion in the systematic review so that the strength of evidence could be compared across psychosocial factors. Prospective cohort studies are the best observational design for questions of etiology and prognosis. The studies included had a prospective cohort design; a population-based sample (etiological studies in healthy populations); at least 500 participants (etiological studies) or 100 participants (prognostic studies in populations of patients with coronary heart disease); measurements of a psychosocial factor used in at least 2 different study populations; and outcomes of fatal coronary heart disease or nonfatal myocardial infarction or (prognostic studies only) all-cause mortality.

Articles were identified by MEDLINE search (1966-1997), manually searching the bibliographies of retrieved articles and previous review articles, writing to researchers in the field, and checking an in-house bibliographic database. No register of published and unpublished studies

with psychosocial exposures exists, and hand searching of journals was not performed, so there is a serious potential for publication bias. For this reason, as well as the lack of standardized methods for measuring psychosocial factors, we carried out a narrative, rather than a quantitative, systematic review. Given that randomized, controlled trials, at least for primary prevention, are rarely feasible, observational studies are likely to remain the main type of evidence on which to base preventive action.

EVIDENCE FOR SPECIFIC PSYCHOSOCIAL FACTORS

Largely on the basis of studies of middle-aged men (Table 1), four groups of psychosocial factors were identified by using the predefined quality filter: psychological traits (type A behavior, hostility), psychological states (depression, anxiety), psychological interaction with the organization of work (job control-demands-support), and social networks and social support. In simple terms, this corresponds to a spectrum, with mainly psychological components at one end and a stronger social component at the other.

Hostility and type A behavior

Type A behavior pattern, the only personality trait that met the criteria of our review, is characterized by hard-driving and competitive behavior, a potential for hostility, pronounced impatience, and a vigorous speech style. The instruments for measuring type A behavior and hostility (the Jenkins Activity Scale, the structured interview, the Minnesota Multiphasic Personality Inventory, and the Bortner Hostility Scale) have been subjected to psychometric testing and incorporated into many cardiovascular cohort studies, including some that have not reported results. Unlike other psychosocial factors, the type A behavior pattern is distinguished by being the subject of numerous intervention trials.[17] On the basis of early positive findings in the Framingham study[18] and the Western Collaborative Group's 8-year follow-up,[19] among other evidence, the National Institutes of Health declared type A an independent risk factor for coronary heart disease. However, with the publication of negative findings,[20-22] it was proposed that a more specific component of type A, namely hostility, might be etiological, although there are conflicting studies. None of the five studies that examined type A or hostility in relation to prognosis among patients with coronary heart disease showed an increased risk; indeed, one suggested a protective effect.

Depression and anxiety

The relation between depression and anxiety and coronary heart disease differs from that of other psychosocial factors for several reasons. First, unlike other psychosocial factors,

Sue Sharples

depression and anxiety represent well-defined psychiatric disorders, with standardized instruments of measurement. Second, depression and anxiety are commonly the consequence of coronary heart disease, and determining the extent to which they are also the cause poses important methodological issues. Third, the ability to diagnose and treat such disorders makes them attractive points for intervention. Finally, depression and coronary heart disease could share common antecedents—for example, environmental stressors and social supports.

Table 2 shows the results from 11 prospective studies that investigated depression or anxiety in the etiology of coronary heart disease, all of which were positive. All three of the prospective studies examining the effect of anxiety in the etiology of coronary heart disease had positive results. Intriguingly, there is some evidence that this effect is strongest specifically for phobic anxiety and sudden cardiac death. Wassertheil-Smoller et al[23] reported the effect of depression in relation to cardiovascular events among 4367 healthy older people. An increase in depression symptoms (but not the baseline scores) predicted events, even when multiple covariates were controlled for. Such findings are compatible with the hypothesis that premonitory signs of coronary heart disease such as angina or breathlessness may have led to the increase in depression. Studies with longer periods of follow-up are less likely to be confounded by the possibility of early disease causing depression but raise further questions about the time course of exposure. For example, it is possible that there is a common trigger (such as viral illness) that precipitates both symptoms of depression and atherothrombotic processes. By examination of subclinical manifestations of coronary heart disease (using noninvasive measures of ar-

Table 1 *Studies of type A behavior, hostility, and coronary heart disease*

Author, year, country	Total sample (% women)	Age at entry, y	Exposure	Follow-up, y	Number of events	Type of events	Adjustments	Relative risk	Summary†
Prospective etiological studies									
Jenkins, 1974[1] USA	2750 (0)	39–59	Type A	4	120	Nonfatal MI and angina	Age	1.8*	+
Rosenman, 1976,[2] USA	3154 (0)	39–59	Type A	8.5	257	Fatal CHD and nonfatal MI	Age, smoking, cholesterol, family history, corneal arcus, schooling, β:α-lipoprotein ratio	2.16*	++
Haynes, 1980[3] USA	1674 (57)	45–77	Type A (Framingham)	8	170	Fatal CHD and nonfatal MI and coronary insufficiency and angina	Age, smoking, blood pressure, cholesterol, glucose intolerance, and other psychosocial factors	1.8*; among men, the effect was confined to white-collar workers	
Shekelle, 1983,[4] USA	1877 (0)	40–55	Hostility (MMPI)	10	139	Fatal CHD and nonfatal MI	Age, smoking, blood pressure, cholesterol, alcohol	1.47*, but effect not linear	+
Cohen, 1985,[3] USA	2187 (0)	57.8 (mean)	Type A (JAS)	8	190	Fatal CHD and nonfatal MI and angina	Smoking, blood pressure, cholesterol, body mass index, alcohol, and other biological factors	1.43; type A associated with prevalence, not incidence or postmortem findings	0
Shekelle, 1985,[6] USA	3110 (0)	46 (mean)	Type A (JAS)	7.1	554	Fatal CHD and nonfatal MI	Age, smoking, blood pressure, cholesterol, alcohol, education	0.87	0
Johnston, 1987,[7] UK	5936 (0)	40–59	Type A (Bortner)	6.2	255	Fatal CHD and nonfatal MI	Age, social class	0.89	0
Ragland, 1988,[8] USA	3154 (0)	39–59	Type A (SI)	22	214	Fatal CHD	Age, smoking, blood pressure, cholesterol	0.98	0
Hearn, 1989,[9] USA	1399 (0)	19	Hostility (MMPI)	33	54	Fatal CHD and nonfatal MI and angina and coronary surgery	Smoking, hypertension, family history	1.1; no association in crude or risk factor adjusted analyses	0
Barefoot, 1995,[10] USA	730 (44)	50	Hostility (Cook-Medley)	27	122	Nonfatal MI	Age, sex, smoking, blood pressure, triglycerides, exercise	1.26 (men) 2.95* (women)	0 (men) ++ (women)
Bosma, 1995,[11] Lithuania and Netherlands	5817 (0)	45–60	Type A (JAS)	9.5	394	Fatal CHD and nonfatal MI	Age	No association	0
Kawachi, 1996,[12] USA	1305 (0)	40–90	MMPI-2 (anger content scale)	7	110	Fatal CHD and nonfatal MI and angina	Age, smoking, blood pressure, cholesterol, body mass index, family history, alcohol	2.66*	++
Everson, 1997,[13] Finland	1599 (0)	42–60	Cynical hostility (Cook-Medley)	6	60	First MI	Age, and biological, socioeconomic, behavioral, and social support factors, prevalent diseases	1.43 (2.18* when adjusted for age only)	0
Tunstall-Pedoe, 1997,[14] Scotland	11,659 (50)	40–59	Type A (Bortner)	7.6	581	Fatal CHD and nonfatal MI and coronary surgery	Age	0.82* in women, ie, type A protective	0
Prognostic studies									
Case, 1985,[15] USA	516 (18) patients <14 days post-MI	<70	Type A (JAS)	2	53	Fatal CHD and all-cause mortality	Age, sex, education, rales, ejection fraction, NYHA functional class, ventricular premature beats	0.8	0
Shekelle, 1985,[16] USA	2314 (11) patients post MI	30–69	Type A (JAS)	3	294	Nonfatal MI and fatal CHD	Smoking, previous MI, angina, fasting glucose level	No association	0
Ragland, 1988,[17] USA	257 (0) with MI or angina	39–70	Type A (SI)	11.5	91	Fatal CHD	Age at initial event, follow-up time, type of initial coronary event, smoking, blood pressure, cholesterol	0.58*; type A protective	0
Barefoot, 1989,[18] USA	1467 (18) patients with angiographic disease	mean 52 (SD 9)	Type A (SI)	5	315	Fatal CVD and non fatal MI	Stratified on clinical prognostic factors	No association with nonfatal MI	0
Jenkinson, 1993,[19] UK	1376 (22) 7 days post-MI	25–84	Type A	3	247	All-cause mortality	Age, previous MI, hospital complications, diabetes, hypertension, car ownership, sex	No association	0

References in this table are given on the BMJ website.
CHD = coronary heart disease; MI = myocardial infarction; JAS = Jenkins Activity Survey; MMPI = Minnesota Multiphasic Personality Inventory; NYHA = New York Heart Association; SI = structured interview.
*$P < .05$.
†0 = no association (relative risk not significantly different from unity); + = moderate association (relative risk, 1.0≤2.0); ++ = strong association (relative risk >2.0).

Table 2 *Studies of depression and anxiety and coronary heart disease*

Author, year, country	Total sample (% women)	Age at entry, y	Exposure	Follow-up, y	Number of events	Type of events	Adjustments	Relative risk	Summary†
Prospective etiological studies									
Hallstrom, 1986,[20] Sweden	795 (100)	38–54	Depression (Hamilton and psychiatric interview)	12	75	Nonfatal MI, angina, and ischemic changes on ECG	Age, social class, marital status, conventional risk factors	5.4*; severity of depression predicted angina but not other outcomes	++
Hagman, 1987,[21] Sweden	5735 (0)	55 (mean)	Anxiety ("stress")	2–7	162	Angina with or without MI	Age, smoking, blood pressure, cholesterol, relative weight	Strong predictor for angina alone	+
Haines, 1987,[22] UK	1457 (0)	40–64	Phobic anxiety (Crown-Crisp)	10	113	Fatal CHD and nonfatal MI	Fibrinogen, cholesterol, factor VII, systolic blood pressure	3.77* for fatal CHD	++
Appels, 1990,[23] Netherlands	3877 (0)	39–65	Depression	4.2	59	Nonfatal MI, unstable angina, and angina	Age, smoking, blood pressure, cholesterol	1.86* for unstable angina for combination of low mood, low energy, hopelessness, poor sleep ("vital exhaustion")	+
Anda, 1993,[24] USA	2832 (52)	45–77	Depression (general well-being)	12	394	Fatal CHD and nonfatal CHD hospitalizations	Age, sex, race, education, marital status, smoking, blood pressure, cholesterol, body mass index, alcohol, exercise	1.6*	+
Aromaa, 1994,[25] Finland	5355 (55)	40–64	Depression (GHQ and PSE)	6.6	91	Fatal CHD	Age, preexisting cardiovascular disease	3.36* (5.52 in those with preexisting cardiovascular disease)	++
Kawachi, 1994,[26] USA	33,999 (0)	42–77	Phobic anxiety (Crown Crisp)	2	168	Fatal CHD and nonfatal MI	Age, smoking, blood pressure, cholesterol, body mass index, diabetes, parental history of MI, alcohol, exercise	3.01* (6.08 when sudden cardiac death examined)	++
Everson, 1996,[27] Finland	2428 (0)	42–60	Hopelessness	6	95	Nonfatal MI	Age, smoking, blood pressure, cholesterol education, income, exercise, alcohol, lipids, social supports, depression	2.05*	++
Wassertheil-Smoller, 1996,[28] USA	4367 (53)	72 (mean)	Depression (CES-D)	4.5	321	Nonfatal MI and nonfatal strokes	Age, smoking, baseline depression, sex, race, randomization group, education, history of stroke, MI, diabetes, and baseline ADL	1.18* per 5-unit increase in depression score (baseline scores) alone did not predict events)	+
Barefoot, 1996,[29] Denmark	730 (44)	50 or 60	Depression (MMPI, obvious depression scale)	27	122	Nonfatal MI	Age, conventional CHD risk factors, baseline CHD	1.7* for 2 SD difference in depression score	+
Kubzansky, 1997,[30] USA	1759 (0)	21–80	Social conditions worry scale	20	323	Fatal CHD, nonfatal MI, and angina	Age, smoking, blood pressure, cholesterol, body mass index, family history, alcohol	1.23* per 1-point increase in social conditions worry scale	+
Prognostic studies									
Ahern, 1990,[31] USA	353		Depression (Beck), anxiety (Spielberger)	12		Fatal CHD	Age, left ventricular dysfunction, previous MI	1.3* for depression	+
Kop, 1994,[32] Netherlands	127 (17) patients 2 weeks after coronary angioplasty	56 (SD 9)	Maastricht questionnaire for vital exhaustion	1.5	29	Fatal CHD, nonfatal MI, further revascularization, increase in coronary atherosclerosis, and new angina	Age, sex, smoking, blood pressure, cholesterol, severity of coronary artery disease, clinical presentation	2.34 ($P = .06$)	+
Ladwig, 1994,[33] Germany	377 (0) 17–21 days after acute MI	29–65	Depression (interview)	0.5		Angina, not returning to work, continuing to smoke	Age, social class, recurrent infarction, rehabilitation, cardiac events, helplessness	2.31* for the effect on angina; depression predicted all outcomes	++
Frasure-Smith, 1995,[34] USA	222 (21) patients 5–15 days after acute MI	24–88	Depression (diagnostic interview schedule)	1.5	21	All-cause mortality and fatal CHD	Age, Killip class, premature ventricular contractions, previous MI	6.64* effect of depression higher in those with (10 premature contractions per hour	++
Barefoot, 1996,[35] USA	1250 (18) patients with angiographic disease	52 (mean)	Depression (Zung)	19.4	604	All-cause mortality and fatal CHD	Disease severity, initial treatment	1.66*, 1.84*, and 1.72* in 3 follow-up periods (year 1, 5–10, and >10, respectively)	+
Denollet, 1996,[36] Belgium	303 (12) patients with angiographic disease	31–79	Type D personality (suppression of emotional distress), depression, social alienation	7.9	38	All-cause mortality and fatal CHD	Left ventricular function, number of diseased vessels, low exercise tolerance, lack of thrombolytic treatment	4.1* for type D and 2.7* for depression	++

References in this table are given on the BMJ website.
ADL = activities of daily living; CES-D = Center for Epidemiological Studies-Depression Scale; CHD = coronary heart disease; ECG = electrocardiogram; GHQ = General Health Questionnaire; MI = myocardial infarction; MMPI = Minnesota Multiphasic Personality Inventory; PSE = Present State Examination.
*$P < .05$.
† 0 = no association (relative risk not significantly different from unity); + = moderate association (relative risk, 1.0≤2.0); and ++ = strong association (relative risk >2.0).

terial structure and function, for example) before the onset of symptoms, the temporal sequence of the relation might be better understood.

Depression in patients after myocardial infarction seems to be of prognostic importance beyond the severity of coronary artery disease. Although discrete major depressive episodes are not uncommon after a myocardial infarction, depressive symptoms are more prevalent. Given the graded relation between depression scores and risk, the long-lasting nature of the effect, and the stability of the depression measured across time, it has been proposed that depression is a continuously distributed chronic psychological characteristic.

Psychosocial work characteristics

The long-standing observation that rates of coronary heart disease vary markedly among occupations (more than can be accounted for by conventional risk factors for coronary heart disease) has generated a quest for specific components of work that might be of etiological importance. The dominant "job strain" model of psychosocial work characteristics, as proposed by Karasek and Theorell, grew out of secondary analyses of existing survey data on the labor force. This model proposes that jobs characterized by low control over work and high conflicting demands might be high strain. A subsequent addition to the model was the idea that social support might buffer this effect. The advantage of the model is that it generates specific hypotheses for testing.

Table 3 shows prospective cohort studies that have examined the relation between job strain and coronary heart disease. Both self-reports and ecological measurements (assigning a score on the basis of job title) of job strain have been made. Self-reports may be biased by early manifestations of disease, and ecological measurements may lack precision. The finding that these methods tend to give reasonably consistent results suggests that they are complementary. Six of the 10 studies had positive results. There is growing emphasis on the importance of low job control rather than on conflicting demands,[24] and it seems likely that these empirical results will lead to a reformulation of the model. Alternative models of psychosocial work characteristics involve an imbalance between the effort at work and rewards received.[25,26]

Social network structure and quality of social support

Social supports and networks relate to both the number of a person's social contacts and their quality (including emotional support and confiding support). Marital status, information that is routinely sought in clinical practice, is a simple measure of social support, and the ability of low social support to predict all-cause mortality has long been recognized. It has been proposed that social supports may act to buffer the effect of various environmental stressors and, hence, increase susceptibility to disease,[27] but most of the evidence supports a direct role.

Five of the 8 prospective cohort studies that investigated aspects of social support in relation to the incidence of coronary heart disease were positive (Table 4). Nine of the 10 prognostic studies were positive, and the relative risks for 3 of these studies exceeded 3.0. Despite the strength and consistency of these findings, the relative effect of structural and functional aspects of social supports has yet to be delineated.

MODIFICATION OF PSYCHOSOCIAL FACTORS

The main implications of these findings for clinical practice are summarized in the box. A recent meta-analysis found that psychosocial interventions are associated with improved survival after myocardial infarction.[28] However, two large, randomized, controlled trials of psychological rehabilitation after myocardial infarction found no difference in anxiety and depression, and this may in part explain the lack of effect on mortality.[29,30] Randomized, controlled trials of modification of social supports after myocardial infarction show a decrease in cardiac death or reinfarction rates.[31] A patient's social circumstances should be elicited as part of the history, and the physician may have a role in mobilizing social support. A multicenter trial of 3000 patients after myocardial infarction (Enhancing Recovery in Coronary Heart Disease) is currently under way in the United States. It will target patients at high psychosocial risk (those who are depressed or socially isolated) and enroll large numbers of women and people from ethnic minority groups.

The potential for primary prevention in relation to psychosocial factors lies largely outside the purview of clinicians. Psychosocial factors themselves are determined largely by social, political, and economic factors, and it is, therefore, policymakers who influence the structure and function of communities--in the public and private domains--who may have scope for primary prevention.

CONCLUSION

Of the large number of psychosocial factors that have been studied, only four met the quality filter criteria: type

Psychosocial components of secondary prevention

Clinicians should consider

Detecting and treating depression

Mobilizing social support

Using socioeconomic status and psychosocial factors to stratify patients by risk

Table 3 *Studies of psychosocial work characteristics and coronary heart disease*

Author, year, country	Total sample (% women)	Age at entry, y	Exposure	Follow-up, y	Number of events	Type of events	Adjustments	Relative risk	Summary†
Prospective etiological studies									
LaCroix, 1984,[37] USA	876 (37)	45–64	Job control or demands (individual and ecological)	10	Not stated	Fatal CHD, nonfatal MI, coronary insufficiency and angina	Age, smoking, blood pressure, cholesterol	2.9* all women (clerical women, RR = 5.2), no association in men; ecological exposure was associated with risk in men and women	+
Alfredsson, 1985,[38] Sweden	958,096 (51)	20-64	Hectic work and few possibilities for learning (ecological)	1	1201	Nonfatal MI (hospitalization)	Age, 10 sociodemographic factors, smoking, heavy lifting	1.5*	+
Haan, 1988,[39] Finland	902 (33) factory workers	20–62	Job control, physical strain, variety (individual)	10	60	Fatal and nonfatal CHD	Age, smoking, blood pressure, cholesterol, alcohol, relative weight	4.95* for low control, low variety, high physical strain	++
Reed, 1989,[40] Hawaii (Japanese ancestry)	4737 (0)	45–65	Job control, demands, and their interaction (ecological)	18	359	Fatal CHD and nonfatal MI	Age	No effect of control, demands or their interaction (nonsignificant trend for lower strain men to have higher CHD)	0
Netterstrom, 1993,[41] Denmark	2045 (0) bus drivers	21–64	Job variety, satisfaction	10	59	Fatal CHD	Age	2.1*; high job variety and satisfaction associated with CHD risk	0
Suadicani, 1993,[42] Denmark	1752 (0)	59 (mean)	Job influence, monotony, pace, satisfaction, ability to relax	3	46	Fatal CHD and nonfatal MI	None	Only inability to relax after work associated with CHD	0
Alterman, 1994,[43] USA	1683 (0)	38–56	Job control, demands, and their interaction (ecological)	25	283	Fatal CHD	Age	1.4 for job strain	0
Bosma, 1997,[44] UK	10,308 (33) civil servants	35–55	Job control, demands (individual, assessed twice 3 years apart, and ecological)	5	654	Angina and physician-diagnosed ischemia	Age, smoking, blood pressure, cholesterol, body mass index, employment grade	1.93*; self-reported or externally assessed low job control predicted CHD	+
Lynch, 1997,[45] Finland	1727 (0)	42–60	Job demands, resources, and income	8.1	89	Fatal CHD and nonfatal MI	Age, behavioral, biological, and psychosocial covariates	1.57* for the effect of high demands, low resources, and low income; 2.59 when adjusted for age only	+
Steenland, 1997,[46] USA	3575 (0)	25–74	Job control and demands (ecological)	14	519	Fatal CHD and nonfatal MI	Age, smoking, blood pressure, cholesterol, education, body mass index, self-reported diabetes	1.41* for low control	+
Prognostic studies									
Hlatky 1995,[47] USA	1489 (24) employed patients undergoing coronary angiography	41–59	Job control, demands (individual)	5	112	Fatal CHD + non-fatal MI prevalence of coronary artery disease	Ejection fraction, extent of coronary atherosclerosis, myocardial ischemia	0.96 for effect of job strain on events. Job strain was associated with normal coronary arteries	—
Hoffman 1995,[48] Switzerland	222 (0) after first MI	30–60	Job work load, locus of control, social supports	1	19	All cause mortality, reinfarction, severe symptoms or poor exercise capacity	Age, severity of MI, exercise	High workload and low external locus of control associated with outcome	+

References in this table are available on the BMJ's website.
CHD = coronary heart disease; MI = myocardial infarction.
*$P < .05$.
†0 = no association (relative risk not significantly different from unity); + = moderate association (relative risk, $1.0 \leq 2.0$); ++ = strong association (relative risk >2.0).

A/hostility, depression and anxiety, work characteristics, and social supports. Although this review cannot discount the possibility of publication bias, the prospective observational studies show etiological roles for social supports, depression and anxiety, and work characteristics and prognostic roles for social supports and depression. Further evidence of a causal role is provided by human and other primate evidence of biological and behavioral pathways mediating these effects. However, conflicting data exist on whether psychosocial interventions reduce mortality after myocardial infarction. This systematic review should be updated and expanded to include other observational study designs and other end points (for example, all-cause mortality) to focus future research and, ultimately, policy.

Table 4 *Studies of social networks and social supports and coronary heart disease*

Author, year, country	Total sample (% women)	Age at entry, y	Exposure	Follow-up, y	Number of events	Type of events	Adjustments	Relative risk	Summary†
Prospective etiological studies									
Medalie, 1976,[49] Israel	10,000 (0)	>40	Perceived love and support from spouse	5	300	Angina	Age, blood pressure, cholesterol, diabetes, ECG abnormalities	1.8*	+
House, 1982,[50] USA	2754 (52)	35–69	Social relationships and activities	11	114	Fatal CHD	Age, baseline CHD, smoking, forced expiratory volume at 1 second	Not stated	+
Berkman, 1983,[51] USA	4725 (53)	30–69	Social network index	9	120	Fatal CHD	Age	2.13*	++
Reed, 1983,[52] USA	4653 (0)	52–71	Social network index	6	218	Fatal CHD and nonfatal	Age, blood pressure, cholesterol, glucose, uric acid, forced vital capacity, body mass index, exercise, alcohol, complex carbohydrate	Social network associated with CHD prevalence, but not incidence	0
Kaplan, 1988,[53] Finland	13,301	39–59	Social network index	5	223	Fatal CHD	Age, smoking, blood pressure, cholesterol, prevalent illness, urban or rural residence	1.34 for men but not women	0
Vogt, 1992,[54] USA	2603 (54)	18–75+	Network scope, network frequency, and network size	15	Not stated	Fatal CHD and nonfatal CHD	Age, sex, socioeconomic status, smoking, and subjective health status at baseline	1.5* for effect of network scope on CHD incidence; all 3 measures predicted survival in those with CHD	+
Orth-Gomer, 1993,[55] Sweden	736 (0)	50	Emotional support from close people and support from extended network (social integration)	6	25	Fatal and nonfatal CHD	Age, cholesterol treatment of hypertension, diabetes, body mass index, smoking physicial activity	3.8* for social integration 3.1 for emotional support	++
Kawachi, 1996,[56] USA	36,624 (0)	42–77	Social network index	4	403	Fatal CHD and nonfatal MI	Age, time period, smoking, blood pressure, cholesterol, diabetes, angina, body mass index, family history, alcohol, exercise	1.14; some evidence for association with fatal CHD (particularly nonsudden cardiac death) rather than nonfatal MI	0
Prognostic studies									
Chandra, 1983,[57] USA	1401	Not stated	Marital status	10	Not stated	All-cause mortality	Age, race, smoking, severity of MI, medical care factors	Married men and women had better in-hospital and 10-year survival	+
Ruberman, 1984,[58] USA	2320 (0) patients with MI	30–69	Social support, life stress	3	128	All-cause mortality, sudden cardiac death	Age, myocardial function, ventricular arrhythmia, smoking	4.5* for the effect of social isolation and high life stress on all-cause mortality; 5.62 for sudden cardiac death	++
Wiklund, 1988,[59] Sweden,	201 (0) patients with first MI	32–60	Social support, depression, and other psychosocial factors	8.3	85	All-cause mortality and recurrent nonfatal MI	Hypertension, smoking, angina	Being single increased risk of death	+
Case, 1992,[60] USA	1234 (38) participants in diltiazem post-MI trial	25–75	Living alone, disrupted marriage	2	226	Fatal CHD and recurrent nonfatal MI	NYHA functional class, ejection fraction, education, no β-blockers, ventricular premature complexes, prior infarction	1.54* for effect of living alone; no effect of marital disruption	+
Hedblad, 1992,[61] Sweden	98 (0) men with ischemic 24-hour ECG	68	Social support and social network	5	17	Fatal CHD and nonfatal MI	Age, smoking, blood pressure, cholesterol, alcohol, exercise, body mass index, triglycerides	5.6* and 4.1* for low informational support and low emotional support, respectively	++
Williams, 1992,[62] USA	1368 (18) patients with angiographic disease	52 (median)	Structural social support (marital status) and functional social support	9	249	All-cause mortality	Age, ejection fraction, noninvasive myocardial damage index, conduction disturbance, pain or ischemic index, mitral regurgitation, number of diseased vessels, % stenosis of left main stem and left anterior descending artery	3.34* for effect of unmarried patients without confidant	++
Berkman, 1992,[63] USA	194 (48) patients with acute MI	65–85+	Emotional support	0.5	76	All-cause mortality	Age, sex, Killip class, ejection fraction, reinfarction, comorbidity, functional disability, previous MI, ventricular tachycardia	2.9* for lack of emotional support	+

Table 4 *Continued*

Author, year, country	Total sample (% women)	Age at entry, y	Exposure	Follow-up, y	Number of events	Type of events	Adjustments	Relative risk	Summary†
Gorkin, 1993,[64] USA	1322 (17) patients with previous MI plus ventricular premature complexes	60.8 (SD 9.9)	Social support	0.8	Not stated	All-cause mortality	Ejection fraction, arrhythmia rates, CHD risk factors	1.46* for 1-point decrease in social support	+
Jenkinson, 1993,[19] UK	1376 (22) 7 days after MI	25–84	Social isolation, life stress, depression, type A personality	3	247	All-cause mortality	Age, previous MI, hospital complications, diabetes, hypertension, car ownership, sex	1.33 for social support; no effect of type A or depression	0
Friedman, 1995,[65] USA	369 (15) patients after acute MI with ventricular arrhythmias in the CAST	63 (SD 9)	Social support, life events, depression, anxiety, type A, anger	1	20	All-cause mortality	Physiological severity, demographic, and other psychosocial factors	Not stated	+

References in this table are given on the BMJ website.
CAST = Cardiac Arrhythmia Suppression Trial; CHD = coronary heart disease; ECG = electrocardiogram; MI = myocardial infarction; NYHA = New York Heart Association.
*$P < .05$.
†0 = no association (relative risk not significantly different from unity); + = moderate association (relative risk, 1.0≤2.0); ++ = strong association (relative risk >2.0).

In this expanding area, future primary research might investigate:

- Interrelationships between different psychosocial factors,
- Effect of change in and cumulative exposure to psychosocial factors,
- Short- and long-term effects throughout life,
- Differences by sex, ethnic group, and country,
- Behavioral and biological mechanisms involved,
- Effect of psychosocial factors on different clinical and subclinical outcomes, and
- Appropriate primary and secondary preventive measures.

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The Last Simple Yo-Yo

Yo-yos are back. Of course, they're high tech now, with shiny plastic, lights, bells, and whistles. Trying to teach my niece the basics of yo-yoing brought back memories. It was 1950—the "happy days." A few of us had televisions, but for most, the entertainment was simple and inexpensive: choose-up touch football, baseball, and basketball games on the school gravel playground and, in the spring, the local yo-yo contests.

For 10 cents, you could purchase a simple Duncan wooden yo-yo at the corner drugstore. When the strings wore out, you could get three new ones for a nickel. We would practice for hours on the playground or at home. Mom always wanted to know where those new, parallel colored marks on the floor, wall, and ceiling came from. The marks on the floor came from practicing "walk the dog," those on the wall from "rock the cradle," and the particularly annoying marks on the ceiling from "around the world."

Remember the first time you tried making the yo-yo "sleep"? No matter what you did, it came right back up to your hand without spinning at the end of the string. It took perfecting a smooth overhand wrist snap to make the yo-yo come to a rest just above the ground. The trick, of course, was to then get it back to your hand. You would try that gentle, reverse wrist motion, but the yo-yo would stop spinning and just lie on the ground. An even harder task was to rewind the yo-yo—not so easy with the "sleeper" string that surrounded the short wooden axle but did not attach (thus allowing the yo-yo to sleep). You soon learned to wrap the string around the axle a few times before attempting the rewind. These days, with the axle made of smooth plastic material, anybody can make the yo-yo sleep.

Having conquered the sleep maneuver, you could try all sorts of other stuff with the yo-yo. To walk the dog, you made the yo-yo sleep and then just touch the floor, where it "walked" forward. A gentle upward wrist movement, and back it came.

Next came around the world. This was a real test of yo-yopersonship. You threw the yo-yo straight out in front of you, and while it was at the end of the string, you swirled it around in a giant circle with a radius equal to the string length. At the end of the circle, you pulled your hand back, and the yo-yo returned home.

The highest level of achievement was rocking the cradle. You made the yo-yo sleep with your right hand, grabbed the string first with the left hand and then the right hand at the one-third and two-thirds marks, respectively, and formed a triangular cradle with the yo-yo hanging down and still sleeping. If you were really good, you released the cradle and allowed the yo-yo to snap back to your hand.

Thus prepared, you entered the school Duncan Yo-Yo Contest. There were nine of us at the start. Four couldn't get their yo-yos to sleep, and they were out. When it came time to walk the dog, two contestants couldn't get the dog back. Two of us remained. The dreaded rock the cradle would determine it all. I snapped the yo-yo into the sleep position and carefully formed the cradle. The yo-yo slept like never before. With a quick snap of my wrist, it came back to my hand—almost perfect. The last yo-yoer made his moves. Everything went perfect. The yo-yo came back up to his hand . . . and he dropped it.

I had won. The Duncan man gave me an emblem, three regular, one small gold, and a magnificent, gleaming black-painted wooden yo-yo with three "diamond cut" glass studs in a row on each side. I was the school champion, the neighborhood hero, the joy of my parents—all for 10 cents and a lot of hard work and practice.

You can buy that expensive high-tech plastic stuff, but I still prefer my inexpensive low-tech wooden one from the mid-20th century! All that fun on a few pennies per day. Somehow, life—and the practice of medicine—was simpler and better.

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MEDICINE CABINET

Topical corticosteroids: back to basics

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Topical corticosteroids are among the most commonly prescribed medications in the ambulatory setting.[1] They are the cornerstones of therapy for a wide variety of dermatoses, such as atopic dermatitis, contact dermatitis, psoriasis, seborrheic dermatitis, and intertrigo.[2,3] In addition, they may also serve as adjuvant or alternative therapy for various other inflammatory, hyperproliferative and pruritic conditions. It is thought that the clinical effects of topical corticosteroids are mediated by their anti-inflammatory, vasoconstrictive, anti-proliferative, and immunosuppressive properties.

WHAT SHOULD BE CONSIDERED IN THE SELECTION OF TOPICAL CORTICOSTEROIDS?

A myriad of topical corticosteroid products is available for the management of dermatoses. A basic understanding of several key factors should help clinicians select appropriate preparations that maximize therapeutic efficacy yet minimize the potential for adverse effects.

In addition to evaluating the relative potency of the active agent, clinicians should consider factors that modulate the clinical efficacy of the selected agent, such as the choice of vehicle, the affected application site, and the use of occlusive dressing.

Potency

Since the introduction of topical hydrocortisone in the 1950s, various topical corticosteroids have been developed to improve the degree of potency. In particular, chemical alterations to the active moeity such as halogenation or esterification have produced intrinsically more potent agents. Topical corticosteroid preparations are categorized according to their relative potency as determined by vasocontrictive assays (Table 1). Keep in mind, however, the vasoconstrictive activity may not always correlate with therapeutic efficacy.[4]

The selection of potency should be based on the responsiveness of the dermatologic condition. Highly responsive dermatosis, such as intertriginous psoriasis or atopic dermatitis, should be treated with weak corticosteroid preparations, whereas less responsive or recalcitrant conditions (for example, palmoplantar or nail psoriasis, lupus erythematosus) often require higher potency agents.[3] When a high potency agent is selected initially to control and arrest the dermatosis, maintenance therapy, if required, should be limited to the lowest effective strength.[5]

Vehicle

The selection of vehicle depends on the type of lesion and the anatomic region that is affected. Most topical corticosteroids are available in many formulations, including ointment, cream, lotion, gel, solution, and aerosol. In addition to being a carrier for the active drug, the vehicle may function to hydrate the skin and augment drug penetration.

Ointments, which consist of oleaginous bases such as petrolatum, provide hydration to the stratum corneum by acting as an occlusive barrier. Penetration of the active agent is therefore enhanced, resulting in improved potency. Ointments are ideal for the management of dry, scaly or lichenified lesions and on areas with thick skin, such as the palms and soles. Emollient creams, which are creams that contain an increased amount of petrolatum, are less greasy and may be more cosmetically appealing to patients than ointments. In general, most creams, lotions and gels are water based and do not significantly provide hydration to the skin. These nonocclusive vehicles are preferable for weeping lesions and for application on hairy areas and flexures. (Note: some preparations are now formulated with an optimized vehicle, resulting in equal potency for ointment, cream, and/or gel formulations.)

Application site

Absorption of topical corticosteroids differs at various anatomic sites. Areas with thick stratum corneum, such as the soles of the feet or palms of the hand, allow for minimal penetration. Consequently, high potency preparations may be required on these areas to ensure a clinical response. Areas such as the scrotum, parts of the face (eyelids in particular), and intertriginous regions permit rapid and extensive drug penetration due to thinner stratum corneum. These areas are therefore more susceptible to adverse effects. The use of low potency preparations is generally preferred in these areas, although recalcitrant conditions (for example, discoid lupus erythematosus and lichen sclerosis) may require higher potency preparations.[4]

Another consideration is the extent of skin involvement requiring topical corticosteroid therapy. Because of increased risk of systemic absorption, low to medium potency preparations are preferable when treating large sur-

Table 1

Relative potency ranking of commonly prescribed topical corticosteroids (adapted from the AHFS[2])

Group I *(Most Potent)*			
Betamethasone dipropionate	Diprolene®, Diprolene® AF	0.05%	Cream, ointment, or gel (optimized vehicle)
Clobetasol propionate	Temovate®	0.05%	Cream or ointment
Diflorasone diacetate	Psorcon®	0.05%	Ointment (optimized vehicle)
Group II			
Amcinonide	Cyclocort®	0.1%	Ointment
Betamethasone dipropionate	Diprosone®	0.05%	Ointment
Desoximetasone	Topicort®	0.25%	Cream or ointment
Desoximetasone	Topicort®	0.05%	Gel
Diflorasone diacetate	Florone®, Maxiflor	0.05%	Ointment
Fluocinonide	Lidex®	0.05%	Cream, ointment, or gel
Halcinonide	Halog®	0.1%	Cream
Group III			
Betamethasone diproprionate	Diprosone®	0.05%	Cream
Betamethasone valerate	Valisone®	0.1%	Ointment
Diflorasone diacetate	Florone®, Maxiflor®	0.05%	Cream
Mometasone furoate	Elocon®	0.1%	Ointment
Triamcinolone acetonide	Aristocort®	0.5%	Cream
Group IV			
Desoixmetasone	Topicort® LP	0.05%	Cream
Fluocinolone acetonide	Synalar® HP	0.2%	Cream
Fluocinolone acetonide	Synalar®	0.025%	Ointment
Flurandrenolide	Cordran®	0.05%	Ointment
Triamcinolone acetonide	Aristocort®, Kenalog®	0.1%	Ointment
Group V			
Betametasone dipropinate	Diprosone®	0.05%	Lotion
Betametasone valerate	Valisone®	0.1%	Cream, lotion
Fluocinolone acetonide	Synalar®	0.025%	Cream
Flurandrenolide	Cordran®	0.05%	Cream
Hydrocortisone butyrate	Locoid®	0.1%	Cream
Hydrocortisone valerate	Westcort®	0.2%	Cream
Prednicarbate	Dermatop®	0.1%	Cream
Triamcinolone acetonide	Kenalog®	0.1%	Cream, lotion
Group VI			
Alclometasone diproprionate	Aclovate®	0.05%	Cream, ointment
Desonide	Tridesilon®	0.05%	Cream
Fluocinolone acetonide	Synalar®	0.01%	Solution

Note: **Group I** represents the super-potent category; potency descends with each group; **Group VII** consist of weak topical corticosteroids such as hydrocortisone, dexamethasone, prednisolone, and methylprednisolone.

face areas.[4] The integrity of the epidermal area should also be evaluated when selecting a preparation to avoid excessive percutaneous corticosteroid absorption.

Occlusive dressings

The use of occlusive dressing to enhance drug potency is less common because of the availability of super potent topical corticosteroids. Application of occlusive dressings, however, such as plastic wraps and hydrocolloid dressings, remains an effective method when treating localized, recalcitrant conditions. The permeability of the drug under occlusive dressing may be increased up to 10-fold.[6]

WHAT IS THE OPTIMAL FREQUENCY OF APPLICATION?

The frequency of application varies with the preparation selected and the condition treated. Traditionally, multiple daily applications have been recommended.[5,7] Recent understanding of drug penetration and deposition, however, suggests less frequent application may be more appropriate owing to the depot effect of the skin. Less frequent application also offers the advantages of reducing the development of side effects and tachyphylaxis, improving patient compliance, and reducing the cost of therapy.[7]

General guidelines developed by American Academy of Dermatology advise once or twice daily applications for most topical corticosteroid preparations. Skin with thick stratum corneum from which the medication is easily removed may require more frequent application; intermittent and intermittent scheduling (for example, every other day, weekends only) may be effective for chronic conditions requiring maintenance therapy.[4] Daily application of nonmedicated emollient creams or ointments may be substituted during the drug-free intervals.[6]

WHAT ARE THE POTENTIAL ADVERSE EFFECTS OF TOPICAL CORTICOSTEROID THERAPY?

Systemic adverse effects

A major concern associated with topical corticosteroid therapy is the risk of systemic absorption. Although they are rare, systemic complications have manifested as a result of topic topical corticosteroid use, such as suppression of the hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, hyperglycemia, growth suppression in children, and femoral head osteonecrosis.[5,8]

Physicians should always keep in mind the conditions that potentiate the risk for systemic absorption: use of high potency preparations of high potency, treatment for prolonged duration, application over large surface areas, addition of occlusive dressing, and use on areas with perturbed skinperturbed skin barrier function. Periodic clinical and laboratory testing may be indicated if the drug is to be used for long periods and/or on large areas of the body.[2] If suppression of the hypothalamic-pituitary-adrenal axis is detected, slow weaning of the topical corticosteroid, reduction of application frequency, or titration to a lower potency preparation is recommended.

Local adverse effects

Local adverse effects, in contrast, are encountered more frequently and have become more prevalent with the introduction of high potency topical corticosteroids. These effects include epidermal and dermal atrophy, striae, purpura, telangiectasia, acneiform eruptions and rosacea. Local hypertrichosis and hypopigmentation may also occur. Although cutaneous adverse effects are generally reversible when treatment is discontinuedupon discontinuation of treatment, atrophic striae may be permanent. Therefore, the use of high potency preparations on delicate areas such as the face should be avoided due to higher risk of local reactions.

Rebound is a rare adverse effect that may occur after using potent topical corticosteroids. Severe exacerbation of the dermatosis may ensue as a result of abrupt discontinuation.[2,5] Rebound erythema may also occur; the discontinuation of topical corticosteroids, which initially cause vasoconstriction, is followed by develop as a result of excessive vasodilation when the drug is withdrawn.[9]

Allergic contact dermatitis to topical corticosteroids may also develop and should be considered in patients with dermatitis that is resistant to therapy. Various components of the preparation (for example, propylene glycol, benzyl alcohol) are common sensitizers.[3] Hypersensitivity to the active steroid moiety itself is also frequentlyhas also been recognized.[10] Clinicians should note that cross-reactivity to other structurally related corticosteroid corticosteroid compounds that are structurally related may occur.[10]

WHAT SPECIAL PRECAUTIONS SHOULD BE CONSIDERED IN PEDIATRIC AND GERIATRIC PATIENTS?

Pediatric patients, in particularly infants, may be more susceptible to the side effects of topical steroids due to their greater skin surface area-to-body weight ratio and fragile skin.[3,11] The most common indication for topical corticosteroids in infants and children is atopic eczema. The use of 1% hydrocortisone is usually sufficient, although a stronger preparation may be indicated for a limited duration during exacerbations.[11] The use of high-potency corticosteroids should generally be avoided in children. Keep in mind, occlusive coverings, such as diapers or tight clothing, may inadvertently increase percutaneous absorption. Geriatric patients, especially those with existing age-related skin atrophy, are also at increased risk for side effects from topical corticosteroids.[3] Similar precautions should be taken when prescribing for elderly patients.

CONCLUSION

As with any prescribed treatment, patient education is essential in optimizing therapy. Patients should be instructed regarding the specific amount of topical corticosteroid to use as well as the proper application techniques. They should also be cautioned against the occlusion of treated area with bandages, dressings, or any other coverings unless specifically directed by the physician. Although topical corticosteroids are frequently used without any untoward effects, the perils of unregulated use should be kept in mind, especially with the availability of newer, super-potent topical corticosteroids.

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Poison ivy, oak, and sumac dermatitis

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The main causes of allergic contact dermatitis in the United States include four commonly encountered species of the Anacardiaceae family: poison ivy (Toxicodendron radicans) (Figure 1) western poison oak (Toxicodendron diversilobum), eastern poison oak (Toxicodendron quercifolium) (Figure 2), and poison sumac (Toxicodendron vernix) (Figure 3). The chief allergenic component, urushiol, is found within the oleoresinous sap of these plants. Urushiol, composed of mixed catechols, is widely distributed throughout the plant, including the leaves, stems, and roots.

Approximately 50% to 70% of the population are sensitized to the toxic effects of these plants.[1] Allergic contact dermatitis primarily results from direct contact with the oleoresin from a portion of a bruised or injured plant. Indirect contact via clothing, shoes, tools, pets, and even smoke from burning plant contaminated with the oleoresin may also elicit a similar reaction.

PRESENTATION

An allergic contact dermatitis develops usually within 24 to 48 hours of exposure in previously sensitized individuals. The dermatitis is characterized by intense pruritis and redness, followed by appearance of papules, vesicles, and bullae in severe cases.[3] These lesions often erupt in multiple, streak-like arrangements suggestive of toxicodendron plant contact. (It should be noted that the fluid contained in these lesions is devoid of antigenic potential.) Dermatitis affecting the face, neck, and genitalia may be accompanied by severe edema.[2]

The course of the dermatitis is usually self-limiting, lasting approximately 1 to 2 weeks. Although most cases resolve without significant sequelae, complications such as secondary bacterial infections, and rarely, erythema multiforme and urticaria may ensue.[2,4]

Daniel Heuclin/NHPA

Figure 1 Poison ivy

Larry West/FLPA

Figure 2 Poison oak

PREVENTION

People who work outdoors or routinely engage in outdoor activities, should take preventive measures such as learning to recognize plants, avoid them and wear protective clothing. Measures to induce tolerance, such as oral or parenteral hyposensitization procedures, remain controversial and are not generally recommended.

Many topical barrier preparations have been investigated as prophylaxis against dermatitis induced by toxicodendron plants. In clinical trials, they have been variably successful in preventing or ameliorating dermatitis that has been produced experimentally.[5] More recently, an organoclay preparation (5% quaternium-18 bentonite) has shown greater efficacy in preventing or limiting reaction to urushiol in susceptible people.[6,7] This lotion (commercially available as Ivy Block®) is applied to the skin at least 15 minutes before anticipated exposure. A visible, clay-like coating appears on the skin indicating areas of protection. The manufacturer recommends repeat application at least every 4 hours for continual protection.

Scott Camazine/OSF

Figure 3 Poison sumac

AFTER CONTACT

Once contact has occurred with the olesoresin, the antigen penetrates the skin rapidly. The oleoresin must be completely removed from the skin within 10 minutes of contact to prevent dermatitis.[1] The affected area should be washed thoroughly with mild soap and water to remove any remaining oleoresin that may be transferred to other areas of the body. Contaminated clothing and gear should also be removed as soon as possible as the antigen remains active on surfaces for a long period of time.

MANAGEMENT

The management of dermatitis induced by toxicodendron depends on the severity and extent of involvement. For patients with mild or moderate, localized presentation, topical measures will usually suffice. Cool compresses using water or diluted aluminum acetate solution (for example, Burow's solution) may alleviate itching and promote drying of lesions. Calamine lotion will similarly impart cool, drying effects. Topical antihistamines and anesthetics are common sensitizers and should be avoided.[8,9]

Topical corticosteroids, when prescribed, are best applied early in the course of the dermatitis to decrease erythema and pruritis. A high-potency preparation may be prescribed for a localized rash whereas a medium-potency preparation should be selected for dermatitis affecting larger areas. The use of occlusive ointments should be avoided on weeping lesions.

In patients with refractory dermatitis or dermatitis associated with extensive involvement or pronounced edema, a course of systemic corticosteroids is indicated. A typical regimen consists of prednisone administered daily orally (1 mg/kg initially) and tapered slowly over 2 to 3 weeks.[2,9] Treatment of shorter duration, using for example prepackaged methylprednisolone dose packs may result in severe rebound exacerbations shortly after discontinuation.[8,10]

In addition to systemic corticosteroids, patients with widespread dermatitis may find symptomatic relief with frequent baths and baths containing colloidal oatmeal (for example, Aveeno®). Oral antihistamines such as diphenhydramine or hydroxyzine may also be considered as adjuvants for their antipruritic, but mostly, sedative effects.

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capsule

The future for endoscopies Refinements to endoscopy are on the way, according to a review in *Endoscopy* (1999;31:557-562), with improvements coming to the lights, the camera, and the assistant. A second angled light added to the endoscope produces more natural images and less glare, which should improve depth perception and therefore ease of performance of minimally invasive techniques; the resolution of the light sensitive charge coupled device at the camera end of the scope continues to improve. And the operator? A robot, naturally.

How accurate is a CT scan in identifying acute strokes?

The short answer - noncontrast cranial computed tomography (CT) is terrible at identifying acute stroke in the first hours after symptom onset.[1,2] Nevertheless, it is the initial imaging method of choice for patients with acute onset of neurologic deficits, because it is readily available in most emergency departments, can be performed rapidly, and is the best method to identify acute hemorrhage or other mimics of acute stroke.[1] In essence, in the first hours after onset of a neurologic deficit, we perform computed tomography to look for everything but ischemic stroke.

The classic hypodensity changes of ischemic infarction may not be visible on a computed tomographic scan until more than 24 hours after the onset of symptoms.[3] Subtle signs of infarction visible in the first few hours after an ischemic stroke include cerebral edema, mass effect (sulcal effacement, ventricle distortion), and loss of the gray-white matter junction.[4,5] In some cases, a hyperdense middle cerebral artery sign, indicative of the thrombus that has induced the stroke, may be visible on computed tomographic images obtained during the first few hours after symptom onset.[4,5] These signs, although helpful when present, typically are not seen on the initial scan, and their absence in no way rules out ischemic stroke.

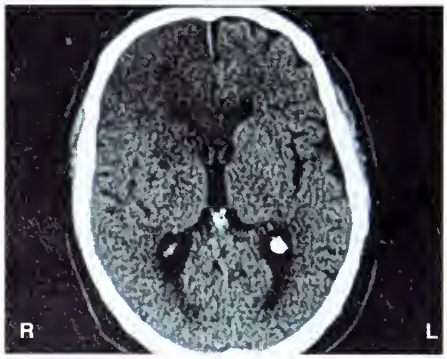

Figure 1 Noncontrast computed tomographic scan in a patient with new onset neurologic deficits shows a hypodensity in the right frontal area. The size and degree of attenuation of this image suggests a large infarct, or an infarct in the subacute (2-21 days) time period.

From 10% to 15% of strokes are hemorrhagic.[1] The majority of this type of stroke are visible on the computed tomographic scan, but it necessitates finding a competent reader to appreciate the finding. A study involving a convenience sample of emergency medicine, general radiology, and neurology physicians revealed that each group had a sensitivity for identifying hemorrhage of 73%, 87%, and 87%, respectively.[6] Thus, not all physicians can reliably identify intracerebral hemorrhage on computed tomographic scans and then safely select candidates for thrombolytic therapy.

Although the signs of ischemic infarction often are not detectable using computed tomography in the first few hours after symptom onset, findings on these initial scans indicative of a large infarct in the territory of the middle cerebral artery must be identified as they represent relative contraindications to thrombolytic therapy.[7-9] Results indicate that a convenience sample of emergency medicine, general radiology, and neurology physicians identified 67% to 93% of large ischemic infarcts.[10] Although experienced neuroradiologists can identify hemorrhage, studies suggest that subtle signs of ischemic infarction may not be identified as reliably. Experienced neuroradiologists achieve complete agreement (interobserver reliability) for the identification of large ischemic infarcts in the territory of the middle cerebral artery (more than one third of the middle cerebral artery territory) on initial computed tomographic scans in 52% to 82% of patients.[4,5,10]

Many other neuroimaging methods are potentially helpful in the evaluation of acute stroke, but magnetic resonance imaging (MRI) is the most common and informative adjunct to computed tomography. Standard T1- and T2 – weighted magnetic resonance imaging sequences identify acute ischemia more predictably and at an earlier time interval from symptom onset than does computed tomographic scanning.[2] Newer magnetic resonance imaging techniques, including diffusion-weighted imaging and perfusion imaging, appear to be even more sensitive and specific in the first few hours after symptom onset than are standard magnetic resonance images.[11] Diffusion-weighted imaging helps clinicians identify 98% of infarcts within a few hours of the onset of ischemia in human studies and is effective at differentiating old from new ischemic infarctions.[12,13] Combining diffusion-weighted imaging with perfusion imaging may provide prognostic information as it identifies both ischemic and irreversibly damaged brain tissues.[12]

Figure 2 Noncontrast computed tomographic scan in another patient with new onset neurologic deficits reveals a left middle cerebral artery territory ischemic infarction. Note the subtle changes including sulcal effacement and loss of the normal gray-white matter junction of the left parietal lobe.

The major downside to magnetic resonance imaging when compared with computed tomographic scanning is that it is more time consuming. For ischemic stroke interventions, such as the administration of tissue plasminogen activator, for which the window of opportunity to begin treatment is 3 hours, it is essential to identify intracranial hemorrhage to avoid morbidity. Computed tomographic scanning is still considered the best means to identify acute hemorrhage, although some authors suggest special magnetic resonance images may be as accurate.[14] In addition, magnetic resonance

imaging is not readily available around the clock at many hospitals, the images are more susceptible to movement artifact, and some patients are precluded from this type of study (eg, because they are too large for the scanner, they have intracranial surgical clips or a pacemaker).

In conclusion, cranial computed tomographic scanning often does not identify early acute ischemic infarction, even when scans are interpreted by expert readers. This method is, however, the best means to rule out acute bleeding and other stroke mimics. As more specific therapies for cerebral ischemia become available, magnetic resonance imaging (diffusion-weighted imaging and perfusion imaging) and magnetic resonance angiography appear promising both for identifying acute strokes and for selecting among interventions.

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RESEARCH TO MAKE YOU THINK

Genetics Determines Your Pain Threshold

Anecdotal evidence has shown that people vary greatly in their sensitivity to pain and in their response to analgesics. Now, new research indicates that there is a genetic basis for differences in pain perception. The findings may lead to a more tailored approach towards determining doses of analgesic and to a better understanding of opiate addiction.

Working with mouse models, scientists from Johns Hopkins University in Baltimore and the National Institute of Drug Abuse identified a candidate gene involved in the regulation of nociception (pain perception) (Proceedings of the National Academy of Sciences USA 1999;14:7752-7755). The gene encodes the mu opiate receptor (mor), the primary target of morphine and other opiates.

The researchers, led by George Uhl of Johns Hopkins University, found that pain perception in mice, as measured by length of time for a response to temperature and pressure stimuli, varied inversely in relation to the density of the mu opiate receptors displayed. The more opiate receptors available, the smaller the response to the stimulus.

Mice that lacked mu opiate receptors had a lower threshold for reacting to pain: they responded to stimuli that were 66% of the strength of the stimulus required to elicit a response in mice with normal mor densities. For mice with half the normal number of receptors, pain reactions occurred when the strength of stimulus was about 80%.

Using eight different strains of mice, through genomic analysis, the researchers then traced the differences in mor density to polymorphisms in the regulatory regions of the mu opiate receptor genes. Several candidate promoter DNA sequences were identified. The promoter is a region of DNA lying upstream of the actual gene to which proteins bind that "promote" the transcription and ultimately the expression of the gene—in this case the opiate receptor. Sequence comparison of the gene encoding the mu opiate receptor showed that it is highly similar between mice and men, suggesting that similar regulatory differences may account for differences in pain perception in humans.

Interestingly, although studies of frontal cortex positron emission tomography in humans have shown that the density of mu opiate receptor varies by up to 50% in individuals, no convincing differences in the ability of receptors to bind with opiates has been shown, so the number of receptors alone may determine pain sensitivity.

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TOOLBOX

Female sexual problems: sexual pain and sexual fears

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Dyspareunia and vaginismus are two common and extremely frustrating sexual dysfunctions for women. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) lists them as two separate disorders in the subcategory of sexual dysfunction.

DYSPAREUNIA

Dyspareunia is recurrent genital pain associated with sexual activity; it can be classified as primary, when pain has always occurred during sexual activity, or as secondary, when it occurs after a period of pain-free lovemaking. The term is usually used to describe pain on penetration, but it can occur during genital stimulation. It is best described according to the site of the pain.

Traditionally, it was thought that superficial dyspareunia (at or around the vaginal entrance) was likely to have a psychogenic origin whereas deep dyspareunia was likely to have an organic cause. These explanations are no longer considered helpful. It is important to try to identify the history of the pain, its site, sort, severity, onset, duration and any other associated factors. Look for any physical abnormalities and discuss their effects on the sexual relationship. It must be remembered that physical signs are not always visible, and vulval histology is sometimes required. It is never enough to suggest that dyspareunia is simply psychological, and it should be looked at medically before any psychological components are considered.

Repeated sexual pain can set up a cycle of pain (Figure 1) in which fear of pain leads to avoidance of the sexual activity that produces it, in turn leading to a lack of arousal, failure to achieve orgasm and loss of sexual desire. This can progress to total avoidance of sexual activity and difficulties in the relationship.

Superficial vulval pain

Superficial vulval pain is common and has many causes. Identifying the cause is difficult, however, and patients often see treatments as frustrating and inadequate. There is a great risk of a patient focusing on the discomfort and repeatedly trying to find answers. She may consider herself misunderstood, and her doctor may become frustrated through failure to find a cure. Although patients are anxious and may be introspective about their symptoms, they seem psychologically "healthy."

Vulval pain can be relapsing and remitting. Experiences of burning, itching, and stinging—with patients describing feeling "inflamed"—are common, and any area of the perineum may be affected. Pain may be felt not only on sexual stimulation but can be present all the time and may be triggered by non-sexual activities such as walking. The main causes are vulvitis, vulvovaginitis, vulvovestibulitis, genital herpes (Figure 2), urethritis and atrophic vulvitis, as well as inadequate lubrication and topical irritants such as spermicides or latex.

Vaginal pain

Vaginal pain is the least common category of dyspareunia, partly because sensory nerve endings are present only in the lower third of the vagina. Pain is mainly experienced at the entrance to the vagina. Common causes are a lack of lubrication, vaginal infection, irritants (spermicides and latex), urethral problems, gynecologic and obstetric interventions (episiotomy), radiotherapy (radiation vaginitis), and sexual traumas.

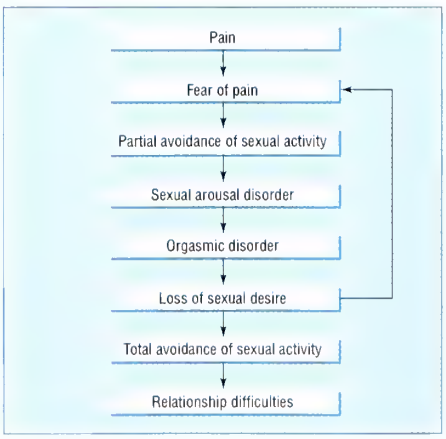

Figure 1 Cycle of sexual pain and avoidance of sexual activity

Figure 2 Small sores on vulva caused by herpes simplex II virus. Genital herpes is a major cause of superficial dyspareunia (Picture by P Marazzi, reproduced with permission of Science Photo Library)

Deep dyspareunia

Deep dyspareunia, often described as pain resulting from pelvic thrusting during sexual intercourse, is also common and has many causes. Major causes include pelvic inflammatory disease; gynecologic, pelvic, or abdominal surgery; postoperative adhesions; endometriosis; genital or pelvic tumors (including fibroids); irritable bowel syndrome; urinary tract infections; and ovarian cysts. A common cause is positional, with deep thrusting by the woman's partner hitting an ovary (equivalent to hitting or squeezing a man's testicle).

Treatment

When considering treatments for dyspareunia, all physical causes should be treated as far as possible. Cognitive behavioral programs can be useful, however, and are similar to the approach used for vaginismus (see below).

Many women, once they understand their sexual problem, can adapt and can achieve good quality sexual activity leading to penetration even though they have a painful physical condition. Successful treatment is in large measure due to the patient feeling that she owns her vagina and controls her sexual activity.

VAGINISMUS

This conditioned response results from associating sexual activity with pain and fear. It is a severe problem for many women, who may experience not only extreme physical pain on attempted penetration, but also severe psychological pain. It consists of a phobia of penetration of the vagina and involuntary spasm of the pubococcygeal and associated muscles surrounding the lower third of the vagina (Figure 3).

Primary vaginismus is diagnosed when a woman has never experienced vaginal penetration, and secondary vaginismus is diagnosed when a woman has had vaginal penetration without a problem in the past. The severity of the symptoms can lead to a general sexual inhibition with avoidance of any sexual touching and, in the most severe cases, to avoidance of any affectionate touching. The spasm can occur not only on attempted penetration, but also on anticipated penetration or during foreplay. At the other end of the spectrum, some women are sexually responsive and have good quality sexual experiences, with imaginative foreplay continuing to orgasm but avoiding penetration.

Attempted penetration leads to pain, fear, humiliation, and frustration, often resulting in feelings of inadequacy and abandonment (Figure 4). The discomfort from repeated attempts at penetration or speculum examination can produce a tightening of muscles in the pelvis, thighs, abdomen, and legs. As well as unsuccessful intercourse, women will have experienced failed gynecologic examinations, difficulty using tampons, and defaulting from attendance for cytology of cervical smears, all of which are almost impossible for them.

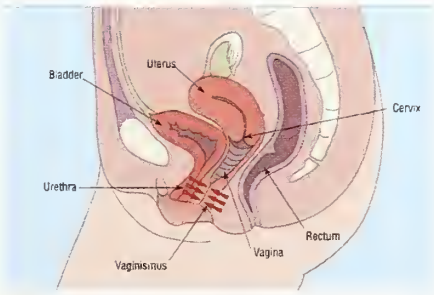

Figure 3 Diagram of vaginismus (Redrawn from Masters WH, Johnson VE, Kolodny RC. Human Sexuality. 5th ed. New York: Harper Collins, 1995)

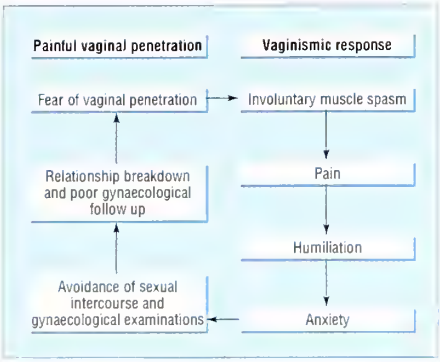

Figure 4 Cycle of vaginismus

Causes

The immediate cause of vaginismus, whether primary or secondary, is the involuntary muscle spasm. Why some women develop vaginismus and others do not is uncertain. The initial response may be secondary to any type of vaginal pain, including all causes of dyspareunia. Experience of physical or sexual abuse can induce phobia of vaginal penetration, as can frightening medical procedures experienced during childhood, painful first sexual intercourse, problems with a relationship, and fear of pregnancy.

Masters and Johnson suggested that important factors might include religious orthodoxy, poor sexual education, sexual inhibition, sexual abuse, rape, and anger in relationships. Other suggested factors include fear of intimacy, pregnancy, or aggression, and the belief that one's vagina is too small (Figure 5). There is a suggestion that psychological conflict can be implicated, in which a woman indirectly expresses anger toward her partner by closing off her vagina.

Treatment

Cognitive behavioral treatment programs for vaginismus comprise a program of relaxation with specific exercises for relaxing the muscles around the vagina combined with a systematic desensitization of the vagina (see box).

Figure 5 Belief that her vagina is too small may be one of the reasons for a woman's fear of vaginal penetration. (Cinesias Entreating Myrrhina to Coition, 1896, by Aubrey Beardsley)

The woman learns to control her vaginal muscle spasm while gently introducing trainers of gradually increasing size into the vagina. Trainers can be fingers, tampons, or specifically designed specula, such as Simms or Amielle (Figure 6). Throughout, the woman is in total control, which gives her great confidence. The program progresses to a point where she is able to share the introduc-

Treating vaginismus

- Sexual education
- Control of vaginal muscles
- Self-exploration of sexual anatomy
- Insertion of a trainer under controlled relaxation
- Sharing of control with partner
- Insertion of penis with the woman in control
- Transfer control of insertion of penis to partner
- Exploration of phobia

Figure 6 Amielle trainers can be used to help overcome fear of vaginal penetration

tion of the trainers with her partner. This stage is followed by insertion of the penis into the vagina with the woman in control (Figure 7).

The phobic element of the problem also needs to be addressed and is often the most difficult part of the treatment. Although women may dread the prospect of the treatment program, the success rate is nearly 100% if they persist with the program. The aim of the treatment is to achieve a situation in which the woman feels that she owns her own vagina and can share it for sexual activity should she wish.

Figure 7 By taking complete control of vaginal penetration, women can learn to overcome their fear of sexual activity (Angelique et Medor from Aretino or The Loves of the Gods, circa 1602, by Agostino Carracci)

Classification of anorgasmia

Primary: Orgasm has never been achieved

Secondary: Orgasm has been achieved in the past

Absolute: Orgasm impossible in all situations

Situational: Orgasm impossible only in certain situations

ANORGASMIA (FEMALE ORGASMIC DISORDER)

The role of orgasm for women is not well defined. For some it is extremely important and sought at every sexual encounter. For others, however, it seems less important and sometimes of little relevance; many women are quite content without it. An important issue is the male partner's understanding of the female orgasm. He often feels that, like him, his partner cannot fully enjoy sexual activity without orgasm, and this can put enormous pressure on the woman to achieve orgasm.

Definition

A working definition of anorgasmia would be an involuntary inhibition of the orgasmic reflex. A woman may have a strong sexual desire with good arousal and enjoy the sensation of the penis in her vagina, but she then holds back even though the stimulation should be sufficient for orgasm. These women often have a strong fear of losing control over feelings and behavior. The fear can be conscious or unconscious, but resolution of the conflict is an important aim of treatment. An example of a situational anorgasmia is a woman who can achieve orgasm by masturbation but not in coupled sexual activity (see box).

Historically, orgasm has been equated with loss of control leading to death, and it has been described as the "mini-death." Most women coming for help feel that having an orgasm will dramatically change their lives. Education and rational discussion is important in disassociating orgasm from its symbolic qualities.

Treatment

Work with both the individual and the couple is aimed at treating the "holding back"—the fear or phobia of orgasm or losing control (see box). Resolution of conflicts (decreasing inhibitions) combined with increasing stimulation is very successful.

A considerable amount of couple work is helpful during which sexual education, sexual myths, and a greater understanding of a partner's needs can be discussed. The question, "Who is this orgasm for?" can be addressed. The idea of difference can be achieved, and the concept of benign variation of sexual need accepted.

Treating anorgasmia

- Self exploration
- Sensate focus
- Masturbation
- Use of adjuncts (vibrators)
- Resolution of unconscious fears of orgasm
- Distraction
- Exercises to heighten sexual arousal
- Transfer to heterosexual situation
- Orgasm on sexual intercourse

Objectives of treatment

- Heightening sexual arousal so that the woman is close to orgasm before penetration
- Enhancing awareness of pleasure and vaginal sensation with tactile stimulation in outer third of the vagina
- Maximizing clitoral stimulation with active thrusting by the woman, woman in superior position, direct clitoral stimulation, use of a vibrator and use of external clitoral stimulation by the woman

100 YEARS AGO

Tonsillectomy makes you smarter

"Careful observation in many of these cases has clearly demonstrated that there is a rapid increase of mental and physical development after removal."

H Bert Ellis, Transactions of the Medical Society of California, 1900

Med.Pix

A red twisted ankle

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QUESTION: A 38-year-old Asian American woman twisted her right ankle by inverting it while walking. Believing that it was a minor sprain, she applied a Chinese medicine patch that was given to her by her mother, who recently emigrated from China. The patient applied the medicine that was impregnated in a patch to the anterior medial and lateral portions of her ankle, leaving the posterior portion uncovered. The following day the patient broke out in a red and painful rash with blisters.

The patient denied fever or any systemic symptoms; when questioned, she did not know the ingredients in the medication. The rash was painful and the lesions made it painful to walk.

Figures 1 and 2 show the patient's ankle at the time of her first visit to the office. Both figures show the erythema has a well-demarcated border, which has been traced by the doctor's pen. The skin is also covered with many small vesicles (< 5 mm in diameter) and at least five large intact bullae (> 5 mm in diameter). What is your diagnosis and how would you manage this patient?

Figure 1

Figure 2

ANSWER: The patient has a severe contact dermatitis to the topical Chinese medicine. Because the ingredients of this medicine are unknown, it is difficult to pinpoint the exact allergen causing the contact dermatitis. Although this patient reports no previous occurrences of contact dermatitis, the recent history and physical examination represent a classic pattern for contact dermatitis. Therefore, no further testing is indicated.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes irritant dermatitis and contact dermatitis due to other substances. This patient has an allergic contact dermatitis, a delayed hypersensitivity reaction that occurs after exposure to an antigenic substance. It is possible that this patient was exposed to this substance as a child in China.

Although irritant dermatitis may look like contact dermatitis, it is not caused by an immunologic mechanism.

The prototypical contact dermatitis is poison oak or poison ivy. These conditions can look similar and are often distinguished by the line of vesicles that can occur from brushing against one of the plants of the Anacardiaceae family. Also the linear pattern occurs from scratching oneself and dragging the oleoresin across the skin with the fingernails. In this case, the erythema and vesicles are widespread and show no linearity. Although irritant dermatitis may look like contact dermatitis, it is not caused by an immunologic mechanism. The substance in irritant dermatitis is purely irritating to the skin and does not serve as an allergen. In patch testing, strong allergic reactions are vesicular, whereas irritant reactions show a deep erythema.

TREATMENT

Use of the Chinese medication was permanently discontinued. Cold compresses and a topical steroid were prescribed. Oral prednisone prescription was considered but not given on the first visit. The patient had no signs of secondary infection that would require antibiotic therapy. She was asked to follow-up 2 days later. When the patient showed no improvement despite use of a class 1, highest potency topical steroid, she was given a 2-week course of prednisone starting with 60 mg daily and tapering down to 5 mg daily. The patient responded rapidly and the condition fully resolved.

Cold wet compresses applied 15 to 30 minutes several times daily relieve symptoms during the acute blistering stage. Topical steroids are not effective in penetrating blisters but may be valuable for the surrounding areas. Aveeno baths may be used to soothe the area and control itching.

If use of systemic steroids is indicated (severe cases or those refractory to topical steroids), there is a choice of oral prednisone or a shot of triamcinolone acetonide (40 mg IM). Oral prednisone doses may vary widely, but a simple dose regimen is 20 mg twice daily for at least 6 days.[1]

Reference

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Building and testing an effective HIV vaccine

About 16,000 people become infected with HIV daily, many of them in the developing world, where standard drug therapy is unaffordable. In the United States and Thailand, phase 3 clinical trials on the efficacy of the bivalent HIV-1 vaccine produced by VaxGen have begun. Although a vaccine may not prevent disease, it could alter the progression of HIV. In these two articles, James Kahn discusses what we know about the vaccine and how it might work and Leslie E Wolf and Bernard Lo explain the ethical dilemmas involved in such trials.

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Competing interests: UCSF receives support for Dr Kahn's research activities from companies that are developing HIV vaccines including: VaxGen, Chiron Corporation, Merck & Co, and Immune Response Corporation. Dr Kahn has no personal financial interests in any of the above companies.

The worldwide epidemic from human immunodeficiency virus (HIV) infection plagues the developed and developing world, devastating rural and urban communities. Among adults in rural and urban sub-Saharan Africa, HIV seroprevalence exceeds 20% and 30%, respectively. The United Nations estimates that 16,000 individuals become infected with HIV daily or 5.8 million persons per year.[1] Each year in the United States, an estimated 40,000 people are infected with HIV. Some estimates suggest that by the end of the decade, more than 40 million people will have died of the complications of HIV infection and 9 million children will have been orphaned as a result of their parents' death from HIV.

WHY DEVELOP AN HIV VACCINE?

In developed countries, antiretroviral medications reduce disease progression and mortality, but developing countries cannot afford standard drug combination therapy, which costs an annual $12,000 per patient. In addition, no treatment will cure a person of HIV infection. With more than 90% of new HIV infections occurring in developing countries and treatment to reduce disease progression practically unavailable as well as not being curative, the most effective way to reduce morbidity and mortality depends on the development of a vaccine that will either abort infection or prevent disease progression for those who do become infected. What are the steps for developing a vaccine?

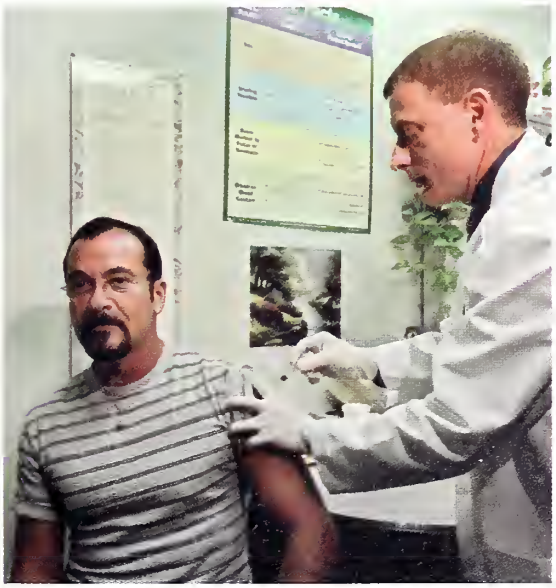
Classic steps for vaccine development have been documented in previous publications and can be broken down into categories (see box).

Summary points

- An HIV vaccine to prevent the consequences of viral infection is key to changing the devastation from the pandemic
- Vaccine development includes careful understanding of how the immune system controls natural viral infection; however, empiricism has always contributed to clinical vaccine development
- An HIV vaccine from VaxGen has entered phase 3 testing in Thailand and the United States
- HIV vaccine participation carries high risk for participants, and we must eliminate stigmatization and other barriers to participation
- The worst outcome for the vaccine study is to fail to answer the research question, necessitating its repetition

PHASE 3 TRIALS IN PROGRESS

In the United States and Thailand, phase 3 clinical trials on the efficacy of the bivalent HIV-1 vaccine produced by VaxGen have begun.[2] These studies have begun at an unparalleled pace considering that acquired immunodeficiency syndrome (AIDS) has been identified as a new syndrome for only18 years and HIV was isolated only 15 years ago. It is the isolation of the virus, the determination of the viral proteins and the sequences that determine viral proteins, along with correctly identifying the mechanism for viral entry into cells, that will accelerate vaccine development. Vaccine trials for other diseases and viruses have been launched without much molecular understanding about the mechanism of vaccine activity. Empiricism and



Eric Risberg/AP

Marty Fenstersheib, a Santa Clara (Calif) Health officer, administers a preventive vaccine against HIV.

Steps in developing a vaccine

- Understanding the pathogenesis of the infection leading to the identification of the causative agent and the factors that lead to disease
- Identifying and applying the technology to safely manufacture a vaccine candidate
- Clinical trials to test the safety (phase 1), activity (phase 2) and efficacy (phase 3) of the vaccine candidate
- Regulatory approval of an effective vaccine
- Widespread implementation of the vaccine with surveillance and monitoring (phase 4)

the needs of the at-risk populations have played key roles for the development of vaccines. VaxGen vaccine studies have begun with a mixture of important scientific milestones accomplished and significant empiricism motivated by the knowledge that the epidemic continues its uninterrupted devastation on entire continents.

HOW DOES THE VACCINE WORK?

Despite the success of non-HIV vaccines (for example, smallpox), we cannot explain why vaccines protect people from disease progression. In addition, it is unlikely that vaccines will prevent infection (available vaccines prevent the consequences of infection). The vaccine from VaxGen (in monovalent or bivalent form) has been safely administered to more than 5,000 people.[4] Its safety has been shown in studies of injection drug users, gay and bisexual men, infants, and heterosexual adults.

Despite not knowing the precise determinates of the immunologic mechanisms necessary to attenuate the virus or to prevent disease progression, the VaxGen vaccine, again administered as a monovalent or bivalent product, shows measurable immunologic responses.[5] The vaccine induces neutralizing antibodies to HIV, blocking antibodies to CD4 and antibodies to the V3 region of gp120 (necessary for binding to the CD4).[6,7] The vaccine candidate also induces IgA antibodies and salivary IgG antibodies in 25% of people vaccinated.[8] Cellular responses specific to CD8 are not often seen. Some investigators suggest that to reduce viral replication effectively, vaccines must induce both cellular (CD8 helper and non-helper responses) and non-cellular responses. Greater practical insight is seen in chimpanzee studies, however, in which animals injected with the vaccine candidate were protected from infection when challenged with a virus homologous to the vaccine antigen.[9]

Phase 3 studies to prove or disprove the efficacy of the candidate vaccine are underway, in part because the vaccine can protect chimpanzees. Thoughtful people may argue that the animal experiment is far removed from sexual transmission and that HIV does not cause disease in chimpanzees. In addition, the vaccine has not been evaluated to determine if it can protect animals following mucosal exposure. The vaccine is safe, however, and effectively induces several types of antibody responses, although little $CD8^+$ cell responses. Whether or not these responses, measured in the laboratory, have much relevance for protection, there is an imperative to move rapidly with safe products such as the VaxGen vaccine that might be effective. So, are there populations to study the vaccine?

There are a number of potential groups on which to investigate vaccine efficacy.[10] The factors that influence a study include the rate of seroconversion among people who are at high risk, the expected protection value of a vaccine compared to placebo, and the rate of people who will be lost to follow-up (or more relevant, the duration of the study). For the ongoing VaxGen study, it was determined that a randomized, placebo-controlled, and double-blind study design is required to prove vaccine efficacy. The study scheme will randomize patients in a 2:1 assignment, meaning that for every three persons who enter the study, two will be randomized into the vaccine group and one into the placebo group.

The rate of seroconversion among persons at highest risk for sexually acquiring HIV is assumed to be 1.5%; the vaccine is predetermined to be important if it is 67.5% better than placebo, and the study is powered, with 90% certainty, to distinguish vaccine efficacy of 67.5%. Data on high-risk HIV-seronegative gay and bisexual men support the HIV sero-incidence calculations. Of 2,189 men enrolled in a sero-incidence study, 59 new infections were observed. This figure represents an annual seroconversion rate of 2.3 per 100 person-years (confidence interval 1.7-2.9).[11] The seroconversion was extraordinarily high among men younger than 25 years of age (4.2 per 100 person-years) compared with men 25 years or older (2.0 per 100 person-years).

The vaccine is administered intramuscularly at the beginning of the study; after 1 month; and at 6, 12, 18, 24, and 30 months of study participation. The duration of the study is 3 years. If the rate of infection is higher than 1.5% per year, or if the vaccine protects against infection with greater efficacy, then the study may be shortened.

REVIEWING THE DATA AND SAFEGUARDING PARTICIPANTS

A Data Safety-Monitoring Board will review blinded data to ensure that one group is not receiving an unanticipated and significantly large benefit or suffering from unanticipated and significantly large toxicity or any other problems associated with participation in this study. We hope that, with counseling to reduce risky behavior, no one will become infected, but we are aware that people will still place themselves at risk for becoming infected with HIV. If people are infected, there are established study-designated

evaluations to determine if vaccination has altered the way the immune system attempts to control the new viral infection.

The study team does not want people to increase their risk for acquiring HIV based on the mistaken assumption that the vaccine has conferred protection.[12] Other areas of concern include the risk of social harm and possible stigmatization.[13,14] For instance, detectable HIV antibodies may not reflect HIV infection and instead reflect vaccine administration. Testing positive for HIV due to vaccine administration could cause harm in terms of obtaining health insurance, travel, or military service. In addition, because participation in a vaccine study is predicated on high-risk behavior, study identification alone carries the risk for stigmatization. Nevertheless, many people at high-risk state that contributing to ending the AIDS epidemic and desires to help others are key factors for participating in a vaccine study.[14-16] Assuming that patients are protected from harm, this study is a failure only if it has to be repeated. The vaccine may not protect against infection. However, the questions of concern that remain are: what happens after infection and can disease progression be reduced?[17] Only long-term follow-up will address these key questions. Ultimately, we all hope that this vaccine or another vaccine candidate will provide an inexpensive and reliable treatment to end the HIV epidemic.

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What about the ethics?

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INTRODUCTION

Clinical trials will be essential to develop an effective HIV vaccine and to stem the devastation of the HIV epidemic. Ethical concerns about research on human subjects have recently been highlighted because of incidents at two academic medical centers.[1-3] Such incidents remind physicians and the public alike of the need for clinical trials to be conducted in an ethically sound manner. As phase 3 trials of HIV candidate vaccines begin, it is appropriate to reflect on the ethical concerns raised by such research. While many of the issues are pertinent to all clinical research, the special characteristics of HIV raise additional ethical concerns.

STUDY DESIGN

The researchers' first ethical obligation is in the design of the research study. The study must be designed to provide valuable information, and the researcher must have reason to believe that the vaccine under trial may work. If these conditions are not met, it is unethical to expose subjects to the risks of participating in the trial.[4] Human trials typically require support from laboratory and animal research. HIV presents some difficulties because a good animal model does not exist, HIV is highly variable and undergoes rapid mutation, and we know little about HIV immunity.[5] Furthermore, it is likely that a vaccine will confer only partial immunity. Because of the gravity of the HIV

epidemic, however, it is ethically appropriate to begin vaccine trials without fully understanding the correlates of viral immunity. Meeting these ethical obligations requires an adequate study size and, because of the relatively low incidence rates of HIV infection, close follow-up.

Researchers must recognize and address the inherent conflict between their obligations to carry out sound research and their obligations to protect their subjects. Trial participants may mistakenly believe that they will receive protection from the vaccine and, therefore, may increase risky behaviors.[6] The study endpoints should, therefore, include not just new infections but also information on risk behaviors. Researchers' obligation to protect their subjects requires that they provide high quality counseling to reduce risk and emphasize the uncertainty about the effectiveness of the candidate vaccine. If counseling were fully effective in reducing risk, however, none of the participants in the trial would seroconvert and there could be no efficacy evaluation. To address the conflict, it may be necessary to have separate counseling and vaccine staff and specific protocols regarding counseling.

THE RESEARCH PARTICIPANT

Informed consent in an HIV vaccine trial presents several difficulties. First, ensuring that consent is truly informed is complicated because participants frequently misunderstand or exaggerate the likelihood that they will receive clinical benefit from the intervention.[6] Second, HIV vaccine trials pose unique risks to participants. Participants may be prevented from participating in future vaccine trials, and vaccines that are developed later may be less effective for them. In addition, because participants may react positively to certain HIV antibody tests, they may also be denied certain governmental jobs (for example, Peace Corps, Foreign Service, military) even if their seroconversion does not represent true infection.[5] Participants in the trial may also face stigmatization from family or friends to whom they disclose information. Because the mere participation in a phase 3 trial will identify the subject as someone at high risk of contracting HIV, it may be impossible to eliminate these risks. While researchers always have an obligation to protect the confidentiality of the information they collect, this duty is particularly important in HIV vaccine trials because of the high risks to participants if confidentiality is breached.

Researchers also must consider their obligations to participants in the trial to provide access to medical care and to any successful vaccine. Some participants will become infected during the vaccine trial. Researchers have an obligation to provide these individuals with medical care, and yet, there has been considerable dispute over whether researchers are obligated to provide state-of-the-art care and, particularly, for international studies, which standard of care should govern.[7-9] Researchers also have an ethical obligation to provide the vaccine to participants in the control group if it is shown to be efficacious. Because the control group has taken on the risk and inconvenience of the trial, it is fair to give them first priority to the benefits of an effective vaccine.

THE COMMUNITY

The interventions in the vaccine trial must be relevant to affected populations. For example, the vaccine candidate should be expected to work against the HIV subtype common to the trial community. Researchers also have an obligation to inform the community about the trial, to respond to misconceptions about the trial, and to ensure that cautionary information is emphasized in any publicity about the trial, to avoid a false sense of security.

CONCLUSIONS

Development of an effective HIV vaccine may be the best chance at stemming the epidemic around the world and in very high-risk groups in the United States. Achieving this goal is likely to require testing of multiple vaccines and, accordingly, the participation of many thousands of research volunteers. This effort cannot be sustained without the support of the affected communities and must be conducted at the highest ethical and scientific levels.

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Training future hospitalists

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THE HOSPITALIST MOVEMENT

The recent emergence of hospitalists has dramatically changed inpatient care in the United States. Hospitalists are physicians based in hospitals who accept patients from primary care physicians upon hospital admission and care for them until they are discharged back to their primary physicians.[1] The newly formed National Association of Inpatient Physicians estimates that there are 3,000 hospitalists in America, a number projected to increase to about 19,000 over the next few years.[2]

Because of their greater experience with hospital care and their availability throughout the day, hospitalists may improve the quality and efficiency of hospital care.[3] Emerging research generally supports this statement. Implementation of a hospitalist model in Pennsylvania that was based in the community was associated with a 14% reduction in hospital charges and a 54% decrease in readmissions.[4] The reorganization of an academic medical service at the University of California, San Francisco, to one employing hospitalists for most inpatient care reduced lengths of stay without compromising clinical outcomes or the satisfaction of patients and house staff.[5] When a multispecialty group based in the community converted to a hospitalist model, it not only improved hospital efficiency but also enhanced outpatient satisfaction, presumably because ambulatory care physicians were more readily available to their clinic patients.[6]

PAST INNOVATIONS IN TRAINING IN INTERNAL MEDICINE

In the 1970s and 1980s, the imbalance between generalists and specialists, skyrocketing costs, and inadequate access to care prompted a reexamination of traditional training methods.[7,8] This led to the setting up of primary care residency programs and tracks to train internists for ambulatory care-based practice. Such programs have produced innovations in ambulatory care and preventive medicine curricula and trained internists who are more likely than their categorical colleagues to practice in primary care settings.[9,10]

Traditional categorical internal medicine programs, challenged to train physicians who may pursue diverse careers in medical subspecialties, biomedical research, or even primary care, have changed less dramatically. The demand for acute care generalists in the growing hospitalist field provides an opportunity for focused curricular innovation in categorical internal medicine residencies, whose graduates comprise the majority of practicing hospitalists. A recent survey of 372 hospitalist physicians showed that 89% were internists, 51% were general internists, and 38% were subspecialists. The rest (11%) trained mainly in family medicine or pediatrics,[11] two additional fields in which these training issues are being raised.

AP/Alan Diaz

Hospitalist practice is now more than just a career choice

Summary points

- The rapid growth in hospitalists presents residents in internal medicine with a new career option as hospital-based generalist physicians
- As well as being clinically competent in inpatient care, hospitalists should understand managed care, health care delivery systems, quality improvement, practice guidelines, subacute care, and end-of-life care
- Within the categorical internal medicine residency at the University of California, San Francisco, we have developed a hospital medicine residency program that includes exposure to hospitalist practices and continuity of care
- Residents also carry out independent research or quality improvement projects, participate in a didactic curriculum, and complete a group project of developing a hypothetical hospitalist system

TRAINING ISSUES FOR HOSPITALISTS

Although most practicing hospitalists are internists, categorical internal medicine residency programs do not require specialized training in the range of issues that hospitalists frequently address. In a survey of the members of the National Association of Inpatient Physicians,[12] practicing hospitalists rated their inpatient training during residency as adequate, but felt that they would have benefited from more formal training in the role of outpatient care

providers and the range of care feasible in the outpatient setting; care in nonacute settings, including skilled nursing facilities and hospice; communication skills; end-of-life care; the business of health care and managed care; and quality improvement and the development of practice guidelines.

A MODEL HOSPITALIST TRAINING PROGRAM

At the University of California, San Francisco, we have developed a hospital medicine track within the categorical internal medicine residency. Our goal is to integrate hospitalist topics into the existing residency curriculum. The core components of the program include an elective in hospital medicine, an independent research or clinical project, mentoring by hospitalist faculty, and inpatient-focused journal clubs. Approximately 10% to 15% of categorical medicine residents elected to participate in the program's first 2 years.

The centerpiece of the hospital medicine track is the elective in hospital medicine in the second and third years of residency (Figure 1). A didactic curriculum emphasizes the knowledge and skills a hospitalist should possess. Residents learn of the financial and organizational impetus for the hospitalist movement. Additional content areas span managed care, communication skills, and business issues for hospitalists. Because hospitalists often play important roles in caring for patients on non-internal medicine services,[11] either as consultants or physicians of record, clinical issues in medical consultation are highlighted. Using the approach of a case-based learning of systems, residents carry out a group project of developing a strategy for the design and implementation of a hypothetical new hospitalist program (Table 1).[13] Leadership skills are developed through seminars focusing on clinical team meetings, the activities of hospital committees, and the design of hospitalist systems.

Residents accompany hospitalists in local inpatient practices. They visit patients and work with multidisciplinary providers at skilled nursing facilities, nursing homes, and during home visits, gaining an appreciation of the capabilities and limitations of these sites of care and of the integral role hospitalists play on the care team (Figure 2).

To develop the analytic and quantitative skills for clinical research, residents can take courses in outcomes research and epidemiology. Most work with a faculty mentor on a research or quality improvement project relevant to inpatient medicine.

Hospitalist elective schedule for residents

	Monday	Tuesday	Wednesday	Thursday	Friday
AM	**1 Seminar:** •Physician workforce issues	**2 Group project†**	**3 Seminar:** •Physician organizations •Public health systems	**4 Independent study**	**5 Seminar:** •Quality improvement •Practice guideline development
PM	Acute care: shadow hospitalist at academic hospital	Observe patient at hospice/ home visit	Shadow hospitalist at academic affiliated community hospital	Continuity patients*	Resident continuity clinic
AM	**8 Seminar:** •Communication with patients and families	**9 Group project†**	**10 Seminar:** •Communicating with healthcare providers	**11 Seminar:** •Physician reimbursement •Implementing a hospitalist system	**12 Seminar:** •Medical malpractice •Billing fraud
PM	Shadow hospitalist at community teaching hospital	Observe patient at hospice/ home visit	Acute care: shadow hospitalist at private hospital	Continuity patients*	Resident continuity clinic
AM	**15 Seminar:** •Palliative care: symptom management •Home IV care	**16 Group project†**	**17 Seminar:** •Medical consultation •Multidisciplinary care	**18 Visiting professor**	**19 Seminar:** •Information systems •Evidence-based medicine
PM	Acute care: shadow hospitalist at community teaching hospital	Observe patient at hospice/ home visit	Shadow hospitalist at public SNF	Continuity patients*	Resident continuity clinic
AM	**22 Seminar:** •DNR* discussions •Assessment of functional status	**23 Group project†**	**24 Seminar:** •Outcomes research	**25 Seminar:** •Dealing with grief •Cross-cultural medicine	**26 Seminar:** •Ethics of end-of-life care •Negotiating a job contract
PM	Acute care: shadow hospitalist at community teaching hospital	Follow patient at hospice/ home visit	Attend multidisciplinary care conference at SNF	Continuity patients*	Resident continuity clinic
AM	**29 Seminar:** •Evaluating patient satisfaction •Evaluating and changing physician behavior	**30 Group project†**	**31 Group project†** Presentation*		
PM			Party		

*Continuity patients = follow patient after discharge from acute care hospital to SNF/hospice/rehabilitation/home.

†Group project = small group meeting for project development.

SNF = skilled nursing facility; HMO = health maintenance organization; IV = intravenous; DNR = do not resuscitate.

Figure 1 A model hospitalist elective month for second-year residents.

Table 1

A case study to enhance business and organizational skills for hospitalists

Problem
You are the medical director of a physician group at a nonteaching hospital in the community. Your hospital has an average daily census of 80 medical patients. Patients are admitted to the hospital by their primary care physicians; each physician has an average of 2 patients in the hospital a day. A few have their office next door to the hospital, but many commute from 10–30 min. About 20% of patients who are admitted have no primary care physicians—their care is provided by a rotating pool of the entire medical staff.

Your hospital competes with a nearby teaching hospital that has house staff to admit patients overnight. Some of your primary care physicians tend to shunt their nighttime admissions to that hospital because of the house-staff coverage. Your board and hospital's chief executive officer have asked you about the potential merits of a hospitalist model of care for your group.

Task
Draft a business plan that considers the following issues:

Business strategy
Describe the services the hospitalists will provide
How is a hospitalist model better than the existing system?
What are the potential disadvantages of a hospitalist model? What are your plans for mitigrating these potential disadvantages?

Organizational strategy
How many hospitalists do you need? support staff? allied health professionals (nurse practitioners, physician assistants)?
Who will employ the hospitalists?
How will the hospitalists be paid?

Strategies for obtaining buy-in
What groups are likely to raise concerns about this new model of care?
How will you convince them of the merits of this system?

Operations strategy
Design a communications system linking hospitalists and primary care providers
Design a coverage system for hospitalists

Accreditation for internal medicine residents, including those in a hospital medicine program, requires them to spend time in a continuity clinic and a minimum of 33% of their time in ambulatory care (Accreditation Council for Graduate Medical Education: www.acgme.org). Even without these requirements, we would maintain the ambulatory care experience for residents in the program. A successful hospitalist career depends on a strong understanding of what can realistically be accomplished in the outpatient setting. Moreover, a significant minority of the nation's hospitalists[11] and all of the faculty hospitalists in the University of California, San Francisco,[14] continue a limited ambulatory care practice.

HOSPITAL MEDICINE: A NEW SPECIALTY?

A new training model raises questions about the specialty status of that field.[15] Hospitalists are acute care generalists defined by the site at which they work. They are qualified to manage medical inpatients and provide consultative services for patients on non-internal medicine services. Hospital medicine shares many attributes with the specialties of emergency medicine and critical care medicine, both of which have successful training programs, separate certification, and full specialty status.

Kelley has argued that any discrete new specialty should also be represented by the existence of departments, divisions, and professional societies with distinct research agendas.[15] Over the past 3 years, clinical hospitalist groups have formed at dozens of academic medical centers, including programs at the Brigham and Women's

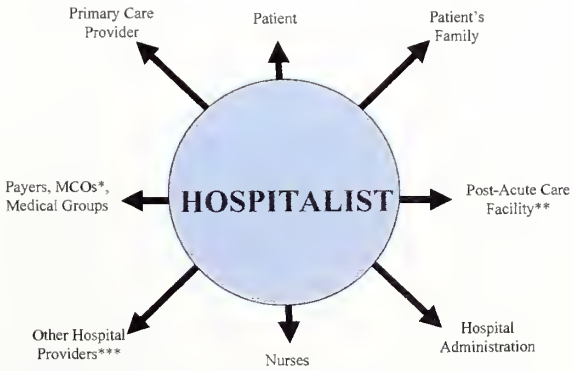

Figure 2 The many faces of hospitalists. Training programs will need to explore each interface to develop future hospitalists' skills.

Hospital, Boston, Mass[16]; University of Pennsylvania School of Medicine, Philadelphia; Emory University School of Medicine, Atlanta, Ga; University of Chicago Pritzker School of Medicine; the Cleveland Clinic, Cleveland, Ohio; and the Mayo Clinic, Rochester, Minn. Areas of expertise for academic hospitalists might include the evaluation and measurement of hospital quality, medical consultation, and the development and implementation of guidelines.

CHALLENGES AND LIMITATIONS

A major obstacle for training programs in hospital medicine is establishing an identity distinct from traditional programs. Opponents of the use of hospitalists argue that fragmentation within internal medicine will lead to outpatient internal medicine becoming indistinguishable from family medicine.[17] We believe that the trend toward outpatient management of increasingly complex disease will secure the niche of outpatient general internists in the care of chronically ill adults.[18]

A central concern raised about hospitalists is the loss of continuity of care. Hospitalist training programs must train hospitalists to communicate effectively with primary care providers. This may improve the situation in many academic centers, in which teaching attending physicians usually serve only one month per year and spend the rest of their time in laboratories or specialized practices. Such physicians, who are not hospitalists,[3] replace primary care providers when patients are admitted to a hospital but may lack the skills and motivation to communicate effectively with primary care providers.

Finally, funding for these innovative curricular changes will be hampered by service requirements and funding restrictions. Research and didactic rotations in which residents do not assume direct patient care may be difficult to suppott with Medicare training dollars. This obstacle can be overcome through independent grants for training programs. Alternatively, money saved by hospitalists who improve the efficiency of inpatient care can be used to support the academic mission of hospitalist groups, including the costs of training.[4,5,19]

EVALUATING HOSPITALIST TRAINING PROGRAMS

Hospitalist training programs must be rigorously evaluated. For our elective course, we survey residents before and after taking the course to explore resident interest in various career paths, including hospital medicine. We ask participants to rate the importance to their future practice of subjects related to hospital medicine, including research design, medical consultation, medical administration, the continuum of care, communication skills, and ethics. We also evaluate perceived preparedness in these areas. Our goal is to determine how the elective affects the residents' self-assessed knowledge and attitudes by comparing responses before with those after taking the elective.

Preliminary results from the first group show that most are interested in careers as hospitalists and that the group's overall self-assessment of preparedness in most subject areas improved after taking the elective.

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COMMENTARY
The joys of being a hospitalist

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Although somewhat controversial in the United States, inpatient specialists or hospitalists are nothing new in other parts of the world. Residents looking for employment must now consider whether to enter a more conventional practice or declare themselves inpatient or outpatient specialists. This is not an easy task.

As a recent graduate of a traditional internal medicine residency, I also faced this decision. During my training in the managed care environment of northern California, I saw firsthand the burgeoning hospitalist movement. As a resident, I rotated through two hospitals operated by a large, successful health maintenance organization (HMO) and the university hospital where the program is based. In my first year, the physicians at the HMO's hospitals observed their own patients during hospital stays. They went through their rounds before, during, and after their busy clinic days, rushing from one patient to the next so as not to get too far behind schedule. The better doctors took time to talk with the patients, the families, and the residents, all the while seeming less harried. By the time I was a senior resident, both facilities had a hospitalist system in place. I rarely saw any of the primary care physicians in the hospital when their patients were admitted. I did, however, see the "inpatient rounders"—the hospitalists—talking to patients and their families and talking with residents.

My career decision was delayed a year because of my stint as a chief resident. My fellow chief residents and I attended on the wards and in the clinic, adding to our experience and knowledge. Meanwhile, I gathered more impressions of the hospitalist system as it matured at the HMO and elsewhere. I talked with friends who worked in the hospital, those who worked in the outpatient clinic, and those who did both. The advantages of the hospitalist system appeared to be the accessibility of the hospitalized patients to their physicians, increased efficiency of the inpatient service, and the freedom of physicians to manage their time. The hospitalists were doing what they wanted to do and were generally a happy group. The patients and primary care physicians also appeared to be satisfied with the system. During that year, I enjoyed my time attending on the wards immensely and began to see how dedicated inpatient internists could become an integral part of the academic mission. It became clear to me that I felt much greater satisfaction caring for inpatients than for outpatients.

Through the year, the advantages of observing patients in and out of the hospital also became clear: being able to offer continuity of care, improved communication between caregivers and patients, and having control over patients' care.

Continuity of care is often cited as the major drawback of the hospitalist system. However, patients change their health care insurance frequently, and many lack a primary care physician, so continuity of care seems to be dwindling anyway; hospitalists are a response, rather than a cause.

Communication between physicians and patients, and among physicians, is the cornerstone of patient care. This is especially true with a hospitalist system in place. The lack of control over patients' care is a tougher issue to address, but again, communication is key if a primary care physician is to have a role in the management of an inpatient. As an inpatient physician, I encourage primary care physicians to contribute to our patients' care. These busy physicians appreciate such efforts but will only accept the role of hospitalists when communication is free and open.

In the end, my decision was simple, as I was given the opportunity to start an academic hospitalist program at the university hospital where I had trained. Although we are sometimes looked upon as deficient physicians, I feel we have carved a niche as conscientious physicians and teachers. Had this opportunity not arisen, however, I would have become a hospitalist in the community and would likely have been as satisfied as I am now.

COMMENTARY
The hospitalist and the care of the patient

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Market-driven forces have dramatically changed the delivery and financing of health services in this country. Among the most controversial departures from traditional practice is the "hospitalist," a new generalist based in hospitals who supplants primary care physicians once their patients have been admitted to a hospital.[1-4]

Conceptually, this program has merits because it addresses the issues of expanding office practice and shrinking hospital load that most generalists now face as the management of more illnesses shifts to the ambulatory setting. Some studies of this model suggest that hospitalists can shorten hospital stays and therefore reduce costs without increasing short-term mortality.[5] These positive reports should interest the short-term investors in managed care, but what about those with long-term interests—patients and primary care physicians? I am reminded of

what Francis Peabody said more than 75 years ago: "The secret of caring for the patient is to care for the patient."

As a family physician in a research medical university, I understand my limitations, appreciate the need for subspecialists, and marvel at the wonders of modern biotechnology. For several years, many family physicians have voluntarily referred their patients with acute myocardial infarctions and other critical illnesses to consultants because the data have shown that care delivered by certain specialists is associated with better outcomes. As such, I am not opposed to consultants taking care of patients nor to the growth of new knowledge-driven subspecialties. But the development of this new model appears to be driven primarily by organizational and financial considerations.

A central tenet of family medicine and primary care is continuous, comprehensive, and personal care. It involves a sustained relationship. Although transferring a patient to a consultant improves outcomes for patients with single severe illnesses, what about those patients who crowd our waiting rooms with multiple chronic diseases intertwined with social problems? If it is mandated that patients be handed over once they become acutely ill, that sustained relationship is severed just when patients may need it most. What about the loss of historical information and trust, so vital to care? How will this mandatory hand off affect end-of-life decisions?

If medicine is seen as a commodity, then this turn toward care that is more specialized may be more efficient in the short term. But if medicine is a social good, this reform could drastically interfere with the aspects of clinical decision making that balance a wait-and-see approach based on a long-term knowledge of patients and an aggressive approach based on technology.

It would be foolish to discard the physician-patient relationship as an anachronism. Yet, I am also a realist and can see benefits in this new approach. Accordingly, several steps should be taken before the hospitalist movement is implemented on any grand scale. First, we need to define what good hospitalists should look like and broaden their perspective to ensure that they think like a primary care physician.[6] Second, additional studies are needed to measure clinical and interpersonal processes as well as clinical outcomes. This will require sophisticated longitudinal studies that attempt to quantify the value of a sustained partnership and the concept of a therapeutic alliance and trust.[7,8]

The best approach might involve a voluntary collaborative model in which a primary care physician obtains a mandatory consultation when a patient is admitted to a hospital and then comanages the patient's care with the hospitalist. This shared care could improve aspects of economic decision making while preserving the physician-patient relationship. In the end, should not the final decision to accept the hospitalist's advice rest with the primary care physician and his or her patients as opposed to those whose sole interest is financial?

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AN INVITATION

We welcome articles up to 600 words on topics such as a memorable patient, a paper that changed your practice, your most unfortunate mistake, or any other piece conveying instruction, pathos, or humor. The article should be supplied on disc and/or emailed to *wjm@ewjm.com.* Permission is needed from the patient or a relative if an identifiable patient is mentioned. We also welcome quotations of up to 80 words (or less) from any source, ancient or modern, which you have enjoyed reading.

Serving native health needs: merging technology and traditional information services

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New Mexico has a unique demographic character, with distinctive health care needs for its population. It has the second largest percentage of ethnic minority population in the United States: 38% Hispanic, 9% American Indian, and 2% African American. With its 25 tribal government entities, New Mexico has the fourth largest American Indian population in the United States and the largest percentage in the lower 48 states.[1] In addition, Albuquerque is one of the largest urban Indian centers in the United States with a population of approximately 20,000 American Indians from over 200 of the 314 tribes found in the lower 48 states.[2] In his opening statement to the US Senate Indian Affairs Committee in April 1996, Michael Trujillo, Director of the Indian Health Service, said, "We must expand our search for partners in the health care arena. To become more efficient and effective, we have to look to foundations, universities, independent organizations and others who can assist us in the delivery of care."[3] This brief report describes how, in order to improve health care statewide, the Health Sciences Center Library of the University of New Mexico through a partnership with the Indian Health Service is using technology to create new knowledge management tools and enhance information services to native populations who, historically, are rural. The implications of the report extend to other regions whose unique populations confront health care providers with special problems and needs.

ABOUT NEW MEXICO

The Health Sciences Center at the University of New Mexico has developed diverse American Indian programs. These programs include: New Mexico Tumor Registry, a registry that has compiled cancer-related data on the American Indian populations in New Mexico and Arizona since 1969; New Mexico Indian Children's Program, a program based in the community that provides supplemental services to Native American children with developmental disabilities and special needs; National Diabetes Prevention Center; and Steering Committee on Native American Psychiatry, which promotes research and teaching of American Indian culture and mental health concepts and provides direct mental health services to New Mexico's Pueblos.

BARRIERS TO SERVICE

As the fifth largest state in area and the fifteenth smallest in population (1.6 million), barriers to service in New Mexico are created by large distances, limited public transportation, language diversity, and few health care facilities. In addition, while Albuquerque is considered among the top 15 hottest job centers in the United States,[4] principally as a result of high technology companies and the national laboratories located in the area, 29 of the state's 33 counties are federally designated Health Professional Shortage Areas.[5] While most of the state's population is enrolled in managed care programs, almost 26% of New Mexicans are without health insurance — the highest percentage in the nation as of 1995.[6] New Mexico has the third largest population of children in poverty[7] and has the second highest percentage of uninsured children.[8] Overall, New Mexico is ranked 44th out of 50 in the list of healthiest states.[9] This unique population also has unique health care problems; for example, the prevalence of diabetes is among the highest in the world,[10] and injuries are the leading cause of death for New Mexicans 45 years of age and younger (with 50% of the accidents involving alcohol).[11] In addition, western medicine is complemented through the use of traditional healers among some American Indian and Hispanic populations.

BREAKING DOWN THE BARRIERS

Over the past 6 years, the University of New Mexico's Health Sciences Center Library has created two unique databases to serve as a resource to the American Indian community and the diverse health care providers and agencies serving them. These databases, available on the World Wide Web, improve access to historical information focused on American Indian health and provide access to up-to-date publications from the Indian Health Service and other federal agencies and linkages to PubMed's MEDLINE citations. The availability of over 5,000 documents spanning more than 200 years provides a rich, unparalleled information resource on health and disease among American Indians. These on-line resources complement the more traditional archival services provided by the Health Sciences Center Library in its New Mexico Health Historical Archives, a special collection that documents and preserves the history of the university and library as well as health care professionals and organizations throughout the state.

The Native Health History Database

The Native Health History Database, funded by the National Library of Medicine, provides indexing and ab-

stracting of more than 3,200 health-related documents published from 1672 to 1965. This Oracle database and its related archival collection include field reports produced by government officials stationed in historic Indian Territory as well as articles published in early medical and anthropological journals. It is accessible at: http://hsc.unm.edu/nhhd.

The Native Health Research Database

The Native Health Research Database was created as a partnership venture between the Health Sciences Center Library and the Indian Health Service. This Web-based database provides bibliographic information and abstracts of health-related articles and resource documents developed primarily by Indian Health Service staff, tribal health professionals, and health care practitioners working on American Indian reservations, Alaska Native villages, and urban areas with significant American Indian and Alaska Native populations. The Native Health Research Database covers from approximately 1966 to the present. Users are able to search by text words (for example, "diabetes"), subjects, authors, or special fields (for example, tribe = "Navajo") to produce tailored information results. The database features some on-line, full-text documents and direct links to reputable American Indian and general health and wellness Web sites. The Oracle database was developed using the SilverStream's Application Software. The database is accessible at: http://hsc.unm.edu/nhrd/.

Although both databases may be useful to primary care providers, the Native Health Research Database, especially, provides primary care physicians with a perspective on patient care that is culturally relevant. A survey of primary care physicians in the Chesapeake Bay area found that 50% of physicians surveyed were interested in getting complementary therapy training in Native American medicine, but only 12.2% had any knowledge of it.[12] This database can help bridge the knowledge gap by providing a single source of articles on western medical practices and traditional native healing. Examples of documents from the Native Health Research Database that have primary care implications include: IHS Primary Care Provider, a government series of articles on health care for Native Americans; a report on a cervical cancer screening and prevention strategy for use among American Indian women[13]; a description of diabetes primary prevention projects in two Native American communities[14]; and a report on Navajo tribal members' use of native healers.[15] Links to tribal programs provide another valuable information resource in addition to published medical journal articles. Physicians can order documents on-line.

Private Collection

ONGOING DEVELOPMENT

Plans to guide the ongoing development of the databases in the future include assessment of Web site usage and statistics and feedback from various advisory groups. A national Native Health Workgroup will be organized to identify baseline health resource needs and requirements of tribes and American Indian organizations. Ongoing workgroup consultation and tribal community partnerships will provide mechanisms to evaluate efforts to address the health information needs and requirements identified by American Indian communities. Offering the databases as core resources, allows the library to play a vital role in establishing and supporting tribal community health partnerships in the new millennium.

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Genes and generalists: why we need professionals with added competencies

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INTRODUCTION

Rapid advances of the Human Genome Project are changing medical practice. Over the past two decades, interdisciplinary national panels of physicians, scientists, lawyers, and ethicists have emphasized the central role of genetic counseling in the field of clinical genetics and, thus, a needed clinical skill for physicians to meet the projected demand from patients for genetic tests.

Physicians must, therefore, strengthen their competencies in providing genetic testing to include pretest education and counseling, written informed consent, and posttest counseling of individuals and families. Genetic testing is different from other forms of medical testing or the diagnosis of most adult diseases because, in many cases, the disorder has not yet developed and the results are relevant to other family members.

Unique issues exist in accurately assessing a patient's risk of developing a disease with a genetic predisposition. Some diseases like familial adenomatous polyposis, caused by a mutation of the APC gene, carry a 100% risk for colon cancer and others, such as hereditary breast-ovarian cancer, have a 50% to 80% risk for cancer occurring. Other important aspects of genetic testing include confidentiality of the test information and the psychological effects of the information on individuals and their families. Therefore, becoming skilled in nondirective counseling and recognizing the value of referral to and collaboration with genetics specialists are vital to physicians and their patients.

Summary points

- Rapid advances of the Human Genome Project are changing medical practice
- Genetic services include genetic counseling, genetic testing, and using genetic information to diagnose and treat medical conditions
- Every national consensus group so far has recommended that nondirective genetic counseling be provided with all genetic testing
- National consensus groups have also recommended that some genetic services be provided by specially trained generalist physicians working with genetics specialists because workforce data reveal a projected shortage of genetics professionals
- Generalist physicians need to enhance their skills in obtaining accurate genetic family histories, doing nondirective counseling, and referring patients to and collaborating with genetics professionals

ESSENTIALS OF GENETIC COUNSELING: NATIONAL RECOMMENDATIONS

Sheldon Reed of the Dwight Institute of the University of Minnesota, Minneapolis, in 1947 coined the term "genetic counseling" to describe the type of genetic social work he provided to families: supportive counseling and genetic information about inheritance patterns and recurrence risks without eugenic overtones.[1] In 1975, the Ad Hoc Committee on Genetic Counseling of the American Society of Human Genetics wrote the most widely used definition of genetic counseling (see box).[2]

Genetic counseling can be performed by one person or a team of professionals and should both precede and follow genetic testing. The Institute of Medicine in 1994 made specific recommendations about genetic counseling

Genetic counseling aims to help the individual or family to

- Comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management
- Appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives
- Understand the alternatives for dealing with the risk of recurrence
- Choose the course of action that seems to them appropriate in view of the patient's risk, family goals, and ethical and religious standards and to act in accordance with that decision
- Make the best possible adjustment to the disorder in an affected family member and/or to the risk of that disorder recurring

that reinforced earlier consensus group statements (Table 1).[3] These recommendations reaffirmed that genetic counseling should be nondirective and must be tailored to the cultural perspective of each patient.

A MODEL FOR GENETIC COUNSELING: HEREDITARY BREAST-OVARIAN CANCER

The Human Genome Project is working out the genetic basis of many common diseases of adulthood. The first step toward prevention and treatment is presymptomatic testing and counseling of persons harboring genes that confer susceptibility. Susceptibility testing for hereditary breast-ovarian cancer is an important model for discussing this new era of genetic medicine.

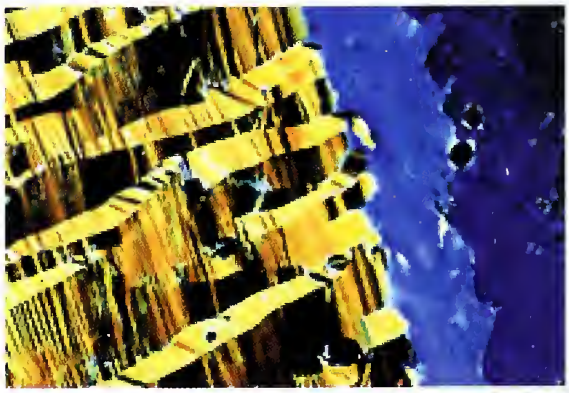
The BRCA1 and BRCA2 genes are tumor-suppressor genes important in regulating the growth of breast epithelial cells; they are responsible for most cases of hereditary breast and ovarian cancer. Few cancers receive the same public attention as breast cancer, in part because it is the second leading cause of death among women aged 25 to 65 years and because the costs are large when the people who develop the disease are young, productive, and often busy raising families and pursuing their careers. The first breast-ovarian cancer susceptibility gene, BRCA1, was isolated in October 1994, and the second such gene, BRCA2, was isolated in December 1995; they are thought to account for about 10% of cases of early-onset, familial breast cancer.[4-6]

In March 1998, the ACP Observer ran a poignant story of a 29-year-old woman with four close relatives, including her aunt and sister, all of whom had had breast cancer or ovarian cancer. The patient approached her newly assigned primary care physician with the desire to receive genetic testing for BRCA1/BRCA2. Her physician, lacking knowledge of the indications for genetic testing, called an oncologist for guidance and obtained information about the commercial laboratory offering genetic testing services. The laboratory required that testing be conducted first with one affected family member, in this case the patient's aunt, followed by testing of the patient and other interested family members. The test results were, in fact, positive for a BRCA1/BRCA2 mutation in the aunt as well as the patient and her sister. The significance of the case was the physician's lack of knowledge and skills in counseling the patient about genetic testing, interpreting the test results, discussing them with the patient and her family members, and collaborating with genetics specialists to develop a management plan. The issue of genetic testing and counseling is, therefore, also important in exposing the need for physicians to acquire new competencies.[7]

Any physician offering BRCA1/BRCA2 genetic testing should be prepared to conduct pretest and post-test counseling that involves a discussion about the natural history of breast cancer, the risk of inheriting a genetic mutation based on the patient's personal cancer history and family history, alternatives to genetic testing—for example, theoretical risk assessment using well-established models[8]—and earlier and more frequent preventive screening with mammography. Physicians should also discuss how the genetic information may be used by the patient in deciding different risk management strategies such as bilateral mastectomy, bilateral oophorectomy, and chemoprevention with tamoxifen citrate, or no intervention. Physicians also must be skilled in obtaining written informed consent, including counseling the patient about possible discrimination in the use of genetic testing information by employers and insurance companies and the psychological effects of the results on the patient and family members.

WHO WILL PROVIDE GENETIC COUNSELING?

Most presymptomatic genetic testing still occurs in research protocols, in which genetic counseling by a qualified genetics professionals is considered mandatory for



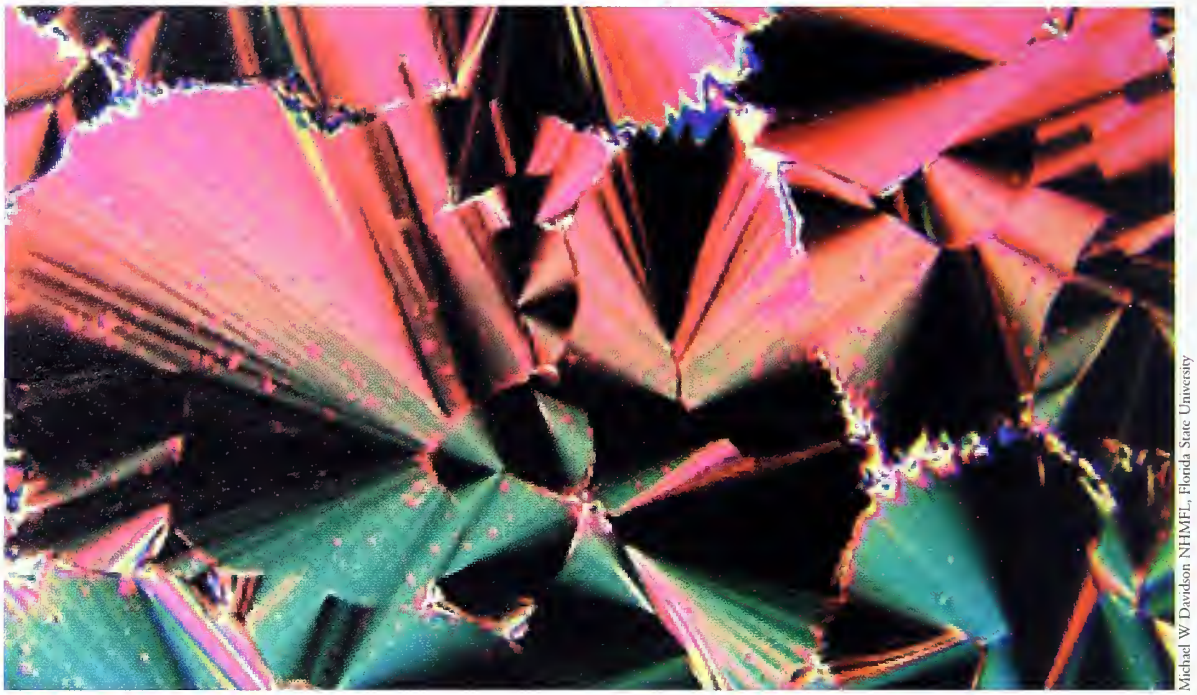
Michael W Davidson, NHMFL, Florida State University

Liquid crystalline DNA

Table 1: *Summary recommendations of national consensus groups*

Principles	The Hastings Center	National Academy of Science	President's Commission	Institute of Medicine
Goals of screening	Improved health in patients with genetic disease Informed reproductive decisions Alleviating anxiety of family at risk	Improved health in patients with genetic disease Informed reproductive decisions Enumeration of genetic disease	Informed reproductive and personal decisions	Informed voluntary reproductive and personal health decisions Screening/testing are viewed as Sources of information
Attainability of goals	Define goals Goals attainable based on pilot studies	Define goals Goals attainable based on pilot studies Standardization of projects	Goals attainable based on pilot studies	Problems should remain investigational until benefits have been defined
Public involvement	Supports community participation in education	Supports public participation Supports involvement of medical community	Supports involvement of medical community	Emphasizes importance of public education Involvement of entire medical community
Access to screening services	Information and screening available for all Priority for high risk groups	Priority for high risk groups	Priority for high risk groups	Equal access and priority to high risk groups, as indicated Recommends expanding third party coverage to the "offering of appropriate genetic testing"
Necessary test characteristics	Precise information to minimize misinterpretation	Acceptable accuracy validity, sensitivity, and specificity	Acceptable accuracy, validity sensitivity and specificity	High test specificity and sensitivity demonstrated through research. Tests to be performed with utmost proficiency and correctly interpreted
Absence of coercion in only obtaining services	Voluntary testing No constraints on childbearing	Voluntary testing	Voluntary testing only newborn screening mandatory only if substantial harm exits	Voluntaries and autonomy are fundamental Mandatory offering of established newborn screening tests
Informed consent	Explicit consent is necessary. Prior to testing clients need to know risks and benefits Ongoing assessment of effectiveness of consent procedure	Explicit consent is necessary Prior to testing clients need to know risks and benefits	Explicity consent is necessary	Full informed consent is an essential element, with delineation of risks, benefits, limitations, other available options, consequences of test results, and disclosure of whether condition tested for is treatable
Protection of subjects	Screening is a form of human experimentation	Screening is a form of human experimentation	Pilot studies are necessary	More research needed, including exploration of psychosocial implications. The only samples that can be used for research purposes are those completely stripped of all identifiers OPRR guidelines to be followed
Disclosure of test results	Full disclosure	Full disclosure	Full disclosure	Full disclosure to individuals tested except in cases of misattributed paternity No disclosure to third parties (insurers/employers) without informed consent
Provision of counseling	Non-directive Define qualifications Ongoing assessment of clients understanding of information and effect information on clients lives	Define qualifications Ongoing assessment of clients understanding of information and effect of information on clients lives	Nondirective Define qualifications Ongoing assessment of clients understanding of information and effect of information on clients lives	Nondirective, patient centered, ethnoculturally sensitive pre-test and post test education and counseling Appropriate trained primary care providers and qualified genetics professionals
Privacy	Information restricted to individual screened	Information restricted to individual screened	Information restricted to individual screened	Confidentiality rigorously protected Information restricted to only individual screened/tested except under rare special circumstances where breach of confidentiality is necessary to avert serious harm
Laboratory provisions	Not specified	Regional facilities Quality control	Regional facilities Quality control	Quality assurance and proficiency program

approval from an institutional review board. As this technology increasingly moves into clinical practice, collaborative teams of genetics professionals, specialists, and primary care physicians will be crucial to offering safe and effective testing. This model of generalists working alongside genetics counselors and geneticists exists throughout the Kaiser Permanente system in California and shows the broad applicability of genetic testing in a managed care population.[9]



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DNA phase transition

Kaiser developed its collaborative model to control costs and to address an increasing shortage of genetics professionals. The American Board of Genetic Counseling recognizes 23 genetic counseling programs at masters level from which about 140 genetic counselors graduate each year.[10,11] At the current level of training, there will be 2,200 genetic counselors at masters level by 2002.[12]

Wilfond and Fost examined the need for professionals trained in genetic counseling in anticipation of large-scale population-based carrier screening for cystic fibrosis.[13] If screening were done annually on 3 million couples who were considering having children, the authors calculated that 561,000 hours would be needed for cystic fibrosis genetic counseling. The Institute of Medicine concluded that generalist physicians must be trained in genetic testing and counseling because the output of genetics professionals will remain inadequate.[3] Hence, initiatives in this rapidly changing field need to be incorporated into continuing medical education.

As genetic tests for conditions with onsets in adulthood continue to emerge in areas such as heart disease and dementia, they will become relevant to a growing number of patients. This will necessitate the development of adjuncts to the labor-intensive and often poorly reimbursed process of pretest education and counseling, such as patient-oriented print material, videotapes, and interactive CD-ROMs. As the public becomes informed, clinicians may be able to spend more time with patients assessing genetic risks, establishing the most effective testing and treatment options, facilitating decision making, and exploring psychosocial issues.

DOCTORS AND PATIENTS: THE CHALLENGING DYNAMICS OF GENETIC COUNSELING

Communication skills and a good physician-patient relationship are important for effective genetic counseling. Emanuel and Emanuel outline four models of the physician-patient relationship. The interpretive model is most appropriate for genetic counseling.[14]

In this interpretive model, the aim of the physician-patient interaction is to elucidate a patient's values and what the patient actually wants. The physician provides information on the nature of the condition and the risks and benefits of possible interventions. Subsequently, the interpretive physicians assist patients in articulating their values and in determining what medical interventions best suit these values. Patients' values are not fixed and may not be known, but often become clear through dialog. This model is also closest to the nondirective model espoused in the genetic counseling literature.[15] In these models, the physician-counselor is more concerned about the process being facilitated than which decision a patient makes.

More recently, Kenen and Smith describe two models of the physician-patient relationship,[16] the first being the mutual participation model advanced in 1956 by Szasz and Hollender.[17] The mutual participation model is most relevant to continuity of care in the primary care setting with the treatment of chronic conditions, where the con-

Table 2

National Society of Genetic Counseling: core competencies for clinicians offering genetic testing

1. Obtain a detailed family history and confirm diagnoses before testing
2. Review the national history of the disease
3. Discuss the predictive value of the test
4. Discuss the risks, benefits, and limitations of testing
5. Explore motivations for requesting testing
6. Discuss readiness for testing and psychosocial issues
7. Describe logistics of testing
8. Present alternatives to testing
9. Discuss confidentiality
10. Outline the process and timing of testing and return of results
11. Provide patient education materials
12. Obtain a written informed consent.

cept of partnership maximizes patients' involvement in decisions and, consequently, enhances compliance to treatment regimens. The goal of the physician is to involve and empower the patient to be an active participant in making decisions about treatment options; patients are encouraged to share concerns so that trust can be established over time.

In the second model, called the "life history narrative model," genetic counselors and client-patients have dual roles. The counselor is both interviewer and listener, and the client is both respondent and narrator. The counselor's main task is to hear the stories that the narrator is telling. The interaction process fosters client power, and the client's beliefs and cognitive perceptions are recognized and valued. With the use of unstructured interviews, clients are encouraged to control the introduction and flow of topics and to openly discuss issues.

This model has been described in the medical encounter literature as patient-centered interviewing, whereby the physician allows the patient to direct the dialog and flow of information.[18,19] The interview begins with the physician asking the patient the reason for the visit and allowing the patient to provide information. Only after the patient has had sufficient time to talk is the physician to enter into the dialog with directed questions about symptoms, illness diagnoses, and treatment options. Research shows that this model of communication enhances empathy and patient satisfaction.[20]

Anticipating the increased use of genetic testing for late-onset disorders in adults, the National Society of Genetic Counselors in 1997 set forth recommendations to assist clinicians in offering genetic testing and counseling.[21] Pretest education and counseling for testing for genetic predisposition for adult-onset conditions, as defined by the National Society of Genetic Counselors, consist of 12 essential steps (Table 2). The National Society of Genetic Counseling further proposed the need for post-test education and counseling to explain the test results and to monitor the need for psychosocial assistance to patients and family members. Generalist physicians now face the challenge of rapidly acquiring these added competencies and integrating them into an already busy clinical practice because the genetic revolution is upon us all.

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News and Features

Viagra makes flowers stand up straight

Judy Siegel-Itzkovich, Jerusalem

Viagra (sildenafil citrate) is good not only for treating male erectile dysfunction. Israeli and Australian researchers have discovered that small concentrations of the drug dissolved in a vase of water can also double the shelf life of cut flowers, making them stand up straight for as long as a week beyond their natural life span.

They have already tested Viagra on strawberries, legumes, roses, carnations, broccoli, and other perishables. In this latest research, they found that 1 mg of the drug (compared with 50 mg in one pill taken by men with erectile dysfunction) in a solution was enough to prevent two vases of cut flowers from wilting for as much as a week longer than might be expected.

Professor Yaacov Leshem, a plant researcher at Bar-Ilan University in Ramat Gan, Israel, and Professor Ron Wills of the food technology department of the University of Newcastle, Australia, also patented a safe, cheap process for increasing the shelf life of fruit, vegetables, and cut flowers using nitric oxide. The produce and cut flowers were fumigated with the colorless, odorless gas, an environmental pollutant that, in minute quantities, acts as the body's most important signalling molecule.

The results of the applied research on nitric oxide were first fully reported in late 1998 in Plant Physiology and Biochemistry (1998; 36:825-833) and have since been the topic of discussion at international conferences of the food storage and packaging industry. Professor Leshem presented his discovery at the international conference on fresh cut produce in England last September.

An unexpected finding of Professor Leshem's group is that Viagra has a similar effect on plant ripening as it does on men's sexual organs. Viagra increases the vase life of flowers by retarding the breakdown of cyclic guanosine monophosphate (cGMP) (the production of which is mediated by nitric oxide).

Both chemicals could provide the food industry with entirely new, dramatically improved processes for preserving agricultural produce, Professor Leshem said. "Nitric oxide is practically free and plentiful, with no identifiable side effects at the very low concentrations we used," he added. "Right now, Viagra costs much more but does have certain advantages over nitric oxide; for example, it's easier to use in cut flowers. It is now up to industry to develop the engineering methods for large scale, pretreatment of produce based on our discoveries."

Kevin Summers/Tony Stone Images

In need of some Viagra?

Pediatricians propose plan to insure every American child

Scott Gottlieb, New York

The American Academy of Pediatrics announced a new health insurance proposal that would create a national program in which all children and young people up to the age of 21 are automatically eligible for full, government-funded healthcare coverage. At present, 11 million children are not covered by insurance.

The new program would have uniform eligibility and benefits, and if enacted, would replace parts of existing programs that provide partial but not complete health insurance coverage, mostly to children born into poor families. The announcement was made at the academy's annual meeting held at the Washington Convention Center in Washington, DC—an event President Clinton attended and at which he offered his own version of health insurance for children during a keynote address.

Under the president's proposal, federal agencies would be directed to visit schools and proactively enroll children into existing federal health insurance programs that the president said are largely underused. Congress created a new program that expanded health insurance to children in

Damien Dovarganes/AP

At least 11 million children are not covered by insurance

1997. It provided $24 billion over 5 years and a total of $39 billion over 10 years, but states have used less than 25% of the money made available so far. "It's simply inexcusable that we've been sitting here with the money for 2 years to provide health insurance to 5 million kids, and 80% of them are still uninsured," President Clinton said during his address to the academy.

The academy's proposal, however, goes further than the president's, and would seek to insure greater numbers of children. Under the academy's proposal, either families could choose to enroll their children in a private insurance plan or they would automatically be enrolled in a national program. This program would require an increased investment in children's health, and the academy said that it was still looking at a variety of ways to fund the proposal. Census Bureau data show that the number of children without health insurance has increased by 15.6% since President Clinton took office, to 11.1 million last year from 9.6 million in 1993. The number of uninsured children rose by 330,000 in 1998 alone, despite an exceptionally robust economy and billions of dollars of new federal money made available to pay for children's health insurance. "The world's most powerful democracy has 11 million uninsured children," said the academy's president, Dr Joel Alpert, in an address he delivered at the annual meeting. "There is no excuse for it. We can solve this problem," he said.

Study leads to a call for an end to spanking

David Spurgeon, Quebec

A Canadian study has shown that adults who reported being slapped or spanked as children were twice as likely as those who did not to have current problems of alcohol or drug misuse and to show antisocial behavior. The study, in the Canadian Medical Association Journal (1999;161:805-809), examined 4888 subjects, ranging in age from 15 to 64 years, none of whom reported a childhood history of sexual abuse or physical abuse, apart from spanking.

Measures included a self-administered questionnaire with a question about frequency of slapping and spanking during childhood, as well as an interviewer-administered questionnaire to measure psychiatric disorder.

The frequency of slapping or spanking varied from "never" (20%) and "rarely" (41%) to "sometimes" (33%) and "often" (6%). Those from the last two groups had significantly higher lifetime rates of anxiety disorders. There was also an association with major depression, but it was not significant.

Linear trend analyses showed significant association between increasing frequency of reported slapping or spanking and increasing rates of lifetime psychiatric disorder. In an accompanying editorial, Murray Strauss of the Family Research Laboratory, University of New Hampshire, wrote: "Ending spanking is a mode of primary prevention to which doctors can make an important contribution." He continued: "This will not be easy, because most doctors, like most patients, believe that spanking is sometimes necessary."

In Canada and the United States, corporal punishment of children by their parents is exempt from prosecution under the criminal code. Dr Strauss says that the current study adds to mounting evidence "that the time has come to end that exception."

Consumer group criticizes surgeon general on ECT

James Ciment, New York

Although still in preliminary draft form and yet to be released officially to the public, the long-awaited surgeon general's report on mental health has already created an uproar, after a consumer health group released excerpts highlighting the efficacy and safety of electroconvulsive therapy in the treatment of depression.

According to the draft report, which cites several clinical studies published between 1993 and 1997, electroconvulsive therapy "is regarded as a safe and effective treatment for depression and is recommended for select groups of patients with severe depression, particularly those with associated active suicidal ideation, psychosis or catatonia." Moreover, the draft report says that the therapy "has the advantage over pharmacotherapy of more rapid resolution of symptoms."

Calling the draft a "blanket endorsement" of electroconvulsive therapy, the National Mental Health Consumers' Self Help Clearinghouse, based in Philadelphia, argues that the surgeon general's office overlooked numerous studies that found electroconvulsive therapy to be more dangerous and less effective than pharmaceuticals for the treatment of severe depression. In a letter to the surgeon general, David Satcher, the Clearinghouse cites numerous studies indicating higher suicide rates for people receiving electroconvulsive therapy compared with those receiving drug treatment, as well as cardiovascular problems, memory loss, and epileptic seizures. In addition, the letter says that the draft report's underestimation of the risks of electroconvulsive therapy means that there is "no opportunity for truly informed consent" as required by law.

The Clearinghouse's executive director, Joseph Rogers, said that his organization released the report because the draft approves of electroconvulsive therapy in such an unqualified way. Calling the report premature and unbalanced, Mr Rogers suspected that both politics and bias were factors in the draft report's uncritical assessment of the therapy. "There was a lot of pressure on the National Institute of Mental Health from the vice president's office," he speculated, "to get this report out after the White House conference [on mental health, held in June]."

In addition, Mr Rogers said, the National Institute's deputy director, Richard Nakamura, is "very pro-electroconvulsive therapy, and I think he is looking for the surgeon general's report to give better legitimacy to electroconvulsive therapy and a clearer and more definitive statement on electroconvulsive therapy."

The surgeon general's office refused to comment on the released draft except to say that it was not final and that it was still undergoing a "rigorous review and revision process."

News brief

New research study to look at link between brain tumors and aspartame

British researchers are to carry out a 3-year study into the relationship between brain tumors and the artificial sweetener aspartame, marketed as Nutrasweet. The study, based at Kings College, London, will look at the possibility that some people have a genetic predisposition to be more sensitive to aspartame than others. Nutrasweet welcomed the study, saying it hoped it would lay to rest the 'groundless rumors' surrounding aspartame, widely used in low-calorie soft drinks and foods.

Nerve gas antidote a possible cause of Gulf war illness

Fred Charatan, Florida

A study conducted over 2 years by the Rand Corporation, a non-profit organization financed by the US Department of Defense, suggests that pyridostigmine bromide may cause a number of symptoms affecting more than 100,000 Gulf war veterans. The 385-page report, written by Beatrice Golomb, professor of medicine at the University of California and physician at the Veterans Affairs Medical Center, San Diego, sharply contradicts two earlier studies—by a presidential advisory committee on Gulf war veterans' illnesses and the Institute of Medicine—both of which ruled out the drug as a cause.

Pyridostigmine bromide, used since 1955 to treat myasthenia gravis, was given to 250,000 to 300,000 US troops in a daily dose of 90 mg for a maximum of 7 days in the Gulf war, as a "pretreatment" against potential Iraqi attacks with the nerve gas soman. The Rand report examined issues surrounding the safety, and to a lesser degree, the effectiveness, of pyridostigmine bromide.

Nerve agents such as soman act by irreversibly binding to and inhibiting the normal action of the enzyme acetylcholinesterase. Acetylcholine is a major neurotransmitter. Acetylcholinesterase breaks down acetylcholine in the synapse; thus the former serves a critical role in regulating nerve signalling. When acetylcholinesterase is inhibited by a nerve agent, an excessive accumulation of acetylcholine occurs in the synapse, followed by excessive binding of acetylcholine to the receptors on the receiving cell. Consequently, cells are overstimulated. This condition leads to an array of possible cholinergic symptoms based on acetylcholine binding to different types of receptors.

Pyridostigmine bromide acts by reversibly binding to and inhibiting acetylcholinesterase on the site where the nerve agent would bind, thus blocking soman from permanently inactivating acetylcholinesterase. As soman is cleared from the body, the drug spontaneously leaves the enzyme and restores functional acetylcholinesterase.

The report concluded that pyridostigmine bromide cannot be ruled out as a possible contributor to the development of unexplained or undiagnosed illness in some Gulf ware veterans. Uncertainties remain about the effectiveness of the drug in protecting people against nerve agents. Bernard Rostker, special assistant for Gulf war illnesses at the Pentagon, said: "We believe this is an important work. It breaks new ground and presents a great deal of information that wasn't available to decision makers during the Gulf war." The report now goes to the Institute of Medicine for final review.

Medicine and Money

Memo

From: Cihak & Glueck, MD executives
To: Chief Executive Officer, Manged Health Care HMO

You directed us to study the effects of cost control and containment procedures, time management, and peer review on the nation's favorite sport of football. We understand that Manged Health is considering buying a professional football team and making it profitable. Being avid sports fans as well as physician executives working for Manged Care, we gladly accepted the assignment. Here are the preliminary findings and suggestions from our study.

Following a scientific protocol, we attended six professional football games. Certain things were obvious after the 3.5 to 4 hours of watching and analyzing each game. Using a highly calibrated stop watch, we determined that each game consisted of only 14.5 minutes of actual playing time, ie, with the ball in play. Even if we round that off to 15 minutes and use the shorter total time of 3.5 hours, this amounts to a 93% inefficiency, with vast waste of time, money, resources and overhead expenses.

Therefore, our first suggestion is to limit all games to 15 minutes from start to finish with no time-outs. Real men don't need time-outs and huddles. Also, why bother with injury time outs unless someone has had a stroke, heart attack or died? After all, in other sports, such as rugby and women's field hockey, there are no injury time outs. The extra 30 seconds can be used to sprint back to the line of scrimmage. These hunks should have no difficulty playing 15 minutes straight. In other sports, they do it all the time.

Second, there is no real need for 47 players on each team when only 11 play at any given time. There are different assortments of players for the offense, defense, punting, kicking off, and field goals as well as the punt return, kick return, and field goal defensive teams for each side. Now, anyone trained in cost containment knows that this causes a great deal of duplication of players. Even the offensive and defensive starters only play a fraction of that 14.5 minutes. Most of the players have had prior experience in playing both ways in Pop Warner, high school, or college. In the good old days when athletes were really tough, they played both ways. Why can't they now?

AP photo/George Nikitin

Are there too many people on the field?

Also, is there really any need for four linemen per team when one guard and one tackle would do? If they played both ways, this would eliminate six of the eight starting linemen for each team. The same could be said for the wide receivers, where one per team would do fine. Do we really need a tight end? Cost containment will cause standard-issue receivers to tighten up enough to meet any possible need, eliminating wasteful duplication. One running back would do as he could just carry the ball twice as often.

Special team players are costly and redundant personnel. Most quarterbacks, being good athletes, could also punt, kick-off, and kick field goals and play on special teams. Alternatively, using practice team and lower quality players should be possible, with no loss of observable quality.

Another way to keep costs under control is to hire more sideline doctors to keep injured players in the game. After all, for the cost of one football player, you can hire 25 or more physicians. They can bandage, stitch up, splint, or cast any minor injuries or fractures, thus minimizing the need for more than 15 players per team. For every injured player the doctors can get back into the game, we can give them a $100.00 bonus as an incentive. Of course, another way to keep costs down, since there are already doctors working for our managed care company, is to require them to use their one Sunday in four off treating players at the game. This would give the injured players access to primary care,

internal medicine, general surgery, and orthopedic surgery with little or no incremental costs to the HMO.

Is there really any need for so many coaches? Every position doesn't need its own coach. Besides, most fans would love to watch a game where the players on the field make the decisions. The game should be played by the athletes not the overage coaches. One head coach would be fine. By eliminating the other dozen or more coaches, as well as the guys in the sky using their charts, telephones, binoculars, and Polaroids, the owners could save on personnel and resources. Yes, there would be on-field mistakes, but so what? These might well make the game more exciting for the casual fan.

The reduction in game time would also save on parking fees, hot-dogs, and souvenirs for the fans. The owners would save on electricity, footballs, clean-up, and other variable expenses. They could pay the referees less for less time. While we are on the subject, the league could limit each game to two footballs and prevent them from flying into the stands by using full stadium wrap around nets. Where does it say the footballs have to be brand new? In fact, recycling is really in now. Since there would be no half time show, this would save on entertainment, band, and cheerleader costs.

By following the above guidelines, the HMO team could save over 90% of their costs, which would mean a much higher profit margin. We initially could lower our ticket prices 10% to hook the fans and subsequently raise them back or higher later on.

While we are seriously considering these cost-saving measures for managed football, wouldn't it be cheaper to manufacture a rounder ball without stitches and made of latex?

These are our initial suggestions with more drastic cuts . . . er, efficiencies and recommendations to follow. One caution, however, is that we will have to be careful that the consumer likes our new product just as much as the old. If the fans object to managed football, we can then allocate a few hundred million dollars to sales, marketing, and advertising to convince them that our product is better and cheaper and good for society. The best way to implement the latter is to hire 100 new marketing people for each new physician hire.

If we tell the patients . . . oops . . . fans, something loud enough, often enough, and long enough, they'll believe it. And if they don't, we can always lobby for government regulations so that they will have to.

Respectively submitted,

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West of the Rockies

Speaker's Corner

Fighting epidemics through the Senate

Once upon a time, contagious diseases were rampant, children died or suffered permanent disfiguration, and everyone knew of the horror of these diseases and lived in fear. Then, ingenious men and women, after working for many years, discovered that immunization would prevent many of these diseases. Society rejoiced and families stood in line waiting for their immunization. Once again, the wonders of modern medicine were proclaimed. Many diseases were nearly eradicated. Epidemics were no longer.

But then as that generation passed, the horrors of epidemics were forgotten. Society had become complacent. No one spoke of disease—not doctors, parents, teachers, or elected leaders. In fact, disease had diminished to the point that many people arose who spoke of the evils of immunization. As immunization rates declined, a few noticed, but their concern fell on deaf ears. Until one day, contagious disease returned and grew into a deadly epidemic. Parents had failed to have their children immunized.

So, what does one do when a college friend asks you to come up with a plan to help protect children from deadly epidemics? You do it, of course. For a number of years, Idaho had hovered at the bottom of the national ranking for immunization rates, and there had been documented pertussis epidemics with loss of life. In the fall of 1998, my college friend Dirk Kempthorne, then a United States Senator, was campaigning for Governor of Idaho and had made children's issues, including improving immunization rates, a high priority. With a landslide win in November 1998, it was time to keep his promise, and he asked me to help.

As the only physician in the Idaho Senate, I had long been concerned with the fact that immunization rates were in the 60% range, especially following the pertussis outbreaks in my hometown. Even after visits by physicians from the Centers for Disease Control (CDC), the medical community seemed to be somewhat lethargic in its response to the epidemic. Meetings were held and data were analyzed. Theories on modern day epidemics were pondered and the efficacy of immunizations was questioned. Plans were made by the CDC to meet again, but not for a year or two. There was no plan of action. It was frustrating to anticipate not meeting again until after yet another epidemic.

Fortunately, however, in the midst of this bureaucracy, our new governor was providing impetus for action. My analysis of the situation in Idaho was that although there were many interested individuals and organizations and an immunization coalition had just formed, a more coordinated approach was needed. We needed a high level leader. Most vaccines in the United States are potentially free to providers through the Vaccines for Children Program, so availability and cost are not issues. Private physicians in Idaho currently give about two-thirds of the immunizations, but often the keeping of handwritten records is sporadic and actual immunization rates are much lower than doctors realize, even within their own practice. Modern Americans are highly mobile, moving from city to city, and also from doctor to doctor. Parents often have trouble finding their own children's shot records. And up until this time there has been no central, computerized record keeping or recall system in place that would encourage and remind parents to obtain immunizations.

My recommendations to the Governor-elect had three main components. Firstly, to appoint a full-time, highly visible leader within the Governor's office; secondly, to create a statewide immunization information system (registry); and thirdly, to expand the newly formed coalition of medical providers, health districts, insurance companies, associations, and interested individuals.

On his first day of work, Governor Kempthorne opened his State of the State address with children's issues and the importance of immunization. A well-respected former director of the Department of Commerce had agreed to head up the immunization challenge. The first component was now

Chris Priest, Mark Clarke/SPL

Immunizations: protection from deadly epidemics

in place. Enthusiasm was high as numerous organizations and insurance companies pledged their support.

The next step proved to be more challenging. Recognizing the vital importance of tracking immunizations and providing a recall system for a mobile population, I introduced a bill to establish within the Idaho Department of Health and Welfare a statewide voluntary registry of immunization status. The bill was introduced in the Senate, where it passed easily out of committee. During floor debate, however, opposition was mounting over the two primary questions of whether it was truly a voluntary system and who would have access to the information. The bill was amended in the Senate to clarify these issues, and it moved to the House. I knew there would be some controversy, but was truly impressed and dismayed by the organized and vocal opposition that had developed.

Numerous individuals had traveled hundreds of miles to testify against the bill. Their concerns focused on both the efficacy of immunizations and the use, or potential misuse, of information gathered by a registry. Due to those concerns, the bill was virtually rewritten during the committee hearing, which lasted 5 hours. As the hearing, which began about 5 pm, moved into the night, the bill was nearly killed on procedural votes several times. But as various concerns were gradually resolved, it was finally sent out of committee to the floor. It took nearly two additional weeks to pass the full House, and in its amended form, the bill returned to the Senate for yet another vote, to approve the amendments. With jeopardy at almost every step, Senate Bill 1183 had finally progressed to the Governor's desk. With his signature, the authority to create a statewide computerized immunization information, tracking, and recall system had been created. The actual development of that system is currently underway.

Creating an energized and coordinated team approach will be the final component needed for success. With the Governor's office in the lead, the Department of Health and Welfare, the seven Health Districts, and an expanding coalition of private associations, advocacy groups, schools, daycare facilities, hospitals, doctors, and insurance companies—all will come together with a common goal—preventing disease and saving the lives of children. By creating a central information system, a comprehensive recall effort will continually take place. Education of parents and immunization providers will spread exponentially. Incentive plans and innovative approaches to delivering immunizations to our children will develop.

Idaho's statewide immunization rate for 2 year olds has already risen from 72% to 79%. Within the year, our goal is to be well above the national average and cross the 80% barrier. Within 2 years of implementation, our goal is to move into the elite immunization range of over 90%. In Idaho, we have the people who have the interest and energy to make these goals a reality. Our goal today should not be to re-invent the wheel, but rather to provide the leadership to a world where the health and safety of our children is truly a high priority.

Sen. Jack Riggs, MD
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What is it like to be a high functioning 60-year-old woman with early onset of Alzheimer's disease?

I am a 60-year-old nurse and writer. In 1997, I started noticing that something was going wrong with my brain. I would lose words. I had sudden episodes of blankness. My short-term memory was shot, and ordinary memory was fragile. Working as a nurse was difficult: I had to double check everything I did. My supervisors warned me that I could be fired if I didn't shape up. My teaching contracts were not renewed. My family noticed I had less energy, that I was suffering from a kind of mental dullness. Then, as my husband started worrying about me, he was diagnosed with prostate cancer. I was shattered. He was only 53 years old.

Keen to find out what was happening to my mind, I volunteered to have neuropsychological testing. The test was debilitating and humiliating. I was exhausted from little sleep. During the test, my brain would go blank.

While I was taking the test, I watched myself taking it. I was doing poorly in task after task. I was horrified. I couldn't do anything right. I began to get angry. I was never able to count 7s backwards. I never could count blocks in staircases. I never did well in math. I felt like I was in the wrong world, the world of male brain cognition, without any recognition of my mental skills gleaned through a lifetime of scholarship and experience.

As I stumbled through the questions, and the tasks went on and on (this was a 6-hour test), I began to question my own capacity to cope not only with the testing skills, but also with my ordinary life as well. I believed the test. I saw, with my own eyes, that I had defects in every realm of mental activity. By the end of the day, I had lost any sense of self-esteem and competency.

The printed report reinforced the grim diagnosis and an even worse prognosis. I had been a vivacious, quick-minded lady. The test said my IQ was in the average range, as were my overall grades. The tester's final opinion was that "the overall pattern of functioning

appears most consistent with an early neurodegenerative process involving visuospatial and memory changes." In plain language, I had early onset Alzheimer's. I had a lethal disease without a cure.

From the beginning, I felt that I was under chronic and severe stress. People do not test well when their brain is swimming with anxiety. I had the double whammy of the multiple stressors in my life. In retrospect, I should have taken out long-term care insurance before doing the test. Now it is in my medical record, set in stone.

When I tried to get insurance, I was told that any mention of memory in a patient's chart is a red flag for the long-term care industry. However, I don't feel that the situation is hopeless. My husband has recovered from prostate surgery and appears to be free of cancer, which removes the worst of the stressors. I continue to lead a stimulating and thoughtful life. I recently took on a new job where I am seen as a valuable resource for the firm.

I am doing all I can to slow down the progression of my disease. I contacted the Alzheimer's Association and followed their behavioral recommendations, from exercise to travel: we went to Italy. This was stimulation of the highest kind.

I take gingko, and vitamin E, and stimulating reading in the hard sciences, which were not my field. I subscribe to Nature, Science, JAMA, and the New England Journal of Medicine and I keep up with the latest progress in Alzheimer's research. I have an electroencephalogram biofeedback machine for treatments at home. I avoid toxic people or environments, and surround myself with loving family and friends.

I've also been invited to enter protocols based on mainstream pharmaceuticals like Arecept, but I have a history of debilitating side effects from strong medicine, so I had to refuse the offers.

Several months ago, I had an advanced magnetic resonance imaging test and recently was given the results. By now, I am getting enured to bad news: according to the anatomical and biological markers, I do have neurodegenerative disease. But according to my neurologist, the lesions and biochemical abnormalities are very minor. And my husband, who is sensitive to every blink, believes that the deterioration over the last 2 years has been slight. People who do not know me do not suspect I have Alzheimer's. Finally, things have been working out. My anxiety and stress are markedly lower. I do get tired in the afternoon, and get a bit confused when I am overstressed. But so do other people who are 60 years old.

Now, my job is to remember that I am still an interesting, intelligent woman who, like other people, gets forgetful sometimes. I must not let labels or tests determine my identity. Writing this essay was not easy; it evoked a lot of pain I would prefer to forget. But if even one person finds a grain of solace from this essay, or understands what it feels like to be in my position, then it will have been worthwhile for me.

A BOOK TO MAKE YOU THINK

Terminal Consent, Michael Freeny, William Austin Press, ISBN 0 9663686 6 5

When George Orwell wrote 1984 in 1949 the free world had just destroyed two totalitarian regimes and still faced another. The idea of Big Brother was all too real, even though the technology that Orwell described was not. Michael Freeny, an American psychologist, has written a novel somewhat like 1984, but this time the technology is all too real, and the threat comes not from a political regime but from the marketplace. The reality of modern information technology makes this book terrifying.

When we pay our bills or use our credit cards, banking machines, and physicians' services, data are gathered. They are used for dozens of purposes, including personal marketing, credit checks, and quality measurement. If all these disparate databases through which our habits are tracked were put into one information system, one would have "MOM," the novel's MultiAxil Outcome Management system.

In this book, a journalist and a psychologist slowly realize that a computer that began as a medical decision aid has grown into a comprehensive manager of millions of individuals' lives. MOM is able to track medical decision making, of course. But the giant insurer that owns the system uses it to track costs of care against the cost of potential lawsuits, to unload doctors who "cost too much," and to skim the cream by avoiding insuring patients with chronic diseases. In addition, Great Health Benefit executives use medical information against politicians seeking to reform the US health care system and sell patients' data to almost anyone. An antiabortion group buys such a list and uses markers for pregnancy and gynecological surgery to find women who have had abortions and then uses that information to extort money from hundreds of thousands of women.

If this scenario seems farfetched, one might look at recent insurance mergers. Aetna gobbled up US Health Care and, just recently, Prudential's health plans. Aetna now insures 22 million people, about 10% of all Americans and 20% of all those covered by private insurance. In its quest to cut costs and ensure profitability for its investors, Aetna will have to use as much information as it can gather legally, and Freeny points out that such data are virtually limitless in our digital age.

Freeny's scenario is terrifying because it is so possible. Unfortunately, his prose and plot do not match Orwell's, or even live up to this book's own theme. Ruthless executives are not only stereotyped but also yell exclamations such as "Darn" and "Heck." The protagonists are likewise stereotyped as purely moral. The plot and its outcome are predictable by the end of the second chapter.

None the less, *Terminal Consent* is an easy but chilling read. The author also offers continuing medical education credits for health professionals. As information systems are synthesised, it would be wise for political leaders to read this book, as well. Who, if anyone, do we trust to use information most judiciously for good? The use of it already has gone beyond individuals, such as doctors, and the debate now is whether it will be managed by government or the marketplace. We should choose soon.

John C Roberts, general internist.
Bellingham, Washington

Letter from Tokyo

Apricot Orchards: Doctors and patients in Japan

Mitchell Feldman Center for AIDS Prevention Studies, Department of Medicine, University of California, San Francisco
Correspondence to: Dr Feldman mfeldman@medicine.ucsf.edu
Work supported in part by a grant from The Japan Foundation.

There is a story of a doctor in ancient China who refused to take money for his services. Instead, he asked that the patient, if satisfied, plant an apricot tree on the hill behind the doctor's cottage. Those treated for minor problems would plant one tree; for treatment of more serious disorders, five trees. Soon the doctor had apricot orchards surrounding his modest cottage. With his fresh apricots, he could trade for rice and other subsistence items and carry on his benevolent practice of medicine.[1]

I came across this story in the library of the International House in Tokyo where I am living during my sabbatical in Japan. I came here to conduct research on HIV/AIDS prevention, reporting policy, and practice. As part of this work, I am visiting clinics and hospitals to understand the doctor-patient relationship. Like many other aspects of Japanese culture, what I see in exam rooms and hear in discussions are both familiar and foreign.

The early Japanese medical system, like much of Japanese culture, was heavily influenced by China. In China, and later in Japan, doctors ideally did not charge directly for their services. Medical practice was seen as a benevolent act (*jin-jutsu*). As Ekken Kuibara, a Japanese Confucian, wrote: "Physicians should always relieve patients suffering without trying to profit."[1] But doctors did not want to depend entirely on the largesse of their patients. Many doctors in Japan preferred to charge for the medications they provided rather than for their services and they came to be called *kushu-shi,* or master of drugs.

The *kushu-shi* model still influences the Japanese health care system. Doctors can both prescribe and sell medication, a potential conflict of interest. Only this year the government made it illegal for the doctor's office and pharmacy owned by the doctor to be under the same roof. Most medications cannot be dispensed for more than 1 month, so even patients with common diagnoses must come in monthly for a brief check-up and another prescription. These visits, often a few minutes each (doctors in private practice see 50 to 100 patients per day), leave little time for discussion. (Even so, life expectancy in Japan is longer than for any other nation—and virtually everyone has some form of health insurance.)

Less is overtly communicated during a typical medical visit in Japan than in the United States, but less may need to be said in a society where trust and dependency more strongly influence social interaction. While dependency, *amae* in Japanese, has negative connotations in the United States, some social scientists contend that it helps hold Japanese society together. *Amae* is more than dependency; it is the unspoken understanding that a person can count on the benevolence of another. In the doctor-patient relationship, it is *amae,* in part, that allows patients to place so much trust in their doctors. A full explanation of the risks and benefits of a particular treatment, for example, may not only be unnecessary, it could lead to concern about the doctor's competence.

But some patients want to be more informed. A recent survey found that almost 70% of Japanese people want to be told if they have cancer and to be included in treatment decisions.[2] Traditionally, many doctors in Japan would not tell patients of a terminal diagnosis.[3] They worried that patients may lose hope and act unpredictably if informed of a terminal diagnosis. I was told of a patient who committed suicide by jumping out of the hospital window after being told that she was being treated not for tuberculosis but for lung cancer. Even the Emperor Hirohito, who died of cancer in 1989, was not told of his diagnosis.

It is the emergence of HIV/AIDS, however, that has helped establish the patients' rights movement in Japan. The Japanese government recently settled a lawsuit with nearly 2000 people with hemophilia infected with HIV by non-heat treated blood products mainly imported from the United States. The Ministry of Health and Welfare admitted that, for 2 years, it allowed the import of these blood products while being aware of the potential risk. This scandal has made more Japanese question their implicit trust in authority and to be more active in making health care decisions.

Changes in the doctor-patient relationship are taking place in Japan and there is already little resemblance to the apricot orchards of old. But change generally takes place more slowly in a society where history is measured in centuries, not decades. It will be some time before it is clear how profound and enduring these changes prove to be.

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All courses listed have been certified as meeting the criteria for Cat 1 of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Cat 1 CME programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

FEBRUARY 13-17, 2000: International Congress 2000 on Endovascular Interventions. The Phoenician, Scottsdale, AZ. 20 hrs Cat 1. Contact Erika Scott, Con (602) 266-2200; Fax (602) 265-8885; escott@azheart.com; www.endovascularcongress.org.

CALIFORNIA, HAWAII, AND NEVADA

All courses and meetings listed are approved for Cat 1 credit toward the CMA Certificate in CME. To list accredited courses here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

JANUARY 21-23, 2000: The 38th Clinical Conference in Pediatric Anesthesiology. The Pediatric Anesthesiology Foundation and Children's Hospital Los Angeles at Disneyland Hotel Anaheim, CA. 13 hrs Cat 1. Contact David J. Steward, (323) 669-2262; Fax (323) 660-8983.

CARDIOLOGY

DECEMBER 17-19, 1999: The 16th Advances in Heart Disease. The Grand Hyatt, San Francisco on Union Square, San Francisco, CA. 16 hrs Cat 1. Contact American College of Cardiology, Registration Secretary, (800) 253-4636, ext. 695; Fax (301) 897-9745.

JANUARY 13-16, 2000: NewEra Cardiac Care 2000: Leading-edge, Minimally Invasive Cardiac Therapies. Coronado Island Marriott Resort, San Diego, CA. Contact Karen Morgan, (760) 751-8841; Fax (760) 751-8842; karen@amainc.com.

JANUARY 21-23, 2000: Clinical Nuclear Cardiology: Case Review with the Experts. American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles, CA. 20 hrs Cat 1. Contact Registration Secretary, Extramural Programs Department, (800) 253-4636, ext 695; Fax (301) 897-9745.

JANUARY 29, 2000: Heart Failure 2000. University of Southern California at Los Angeles Marriott Hotel, Los Angeles, CA. 5 hrs Cat 1. Contact USC School of Medicine, (323) 442-2555 or (800) USC-1119; Fax (888) 665-8650 or (323) 442-2152; usccme@hsc.usc.edu.

NEUROLOGY

JANUARY 21-23, 2000: Neuroscience at its Best: Neurologists and Neurosurgeons: Joint Annual Meeting of the California Association of Neurological Surgeons and the Association of California Neurologists. Grand Hyatt on Union Square, San Francisco, CA. 5.5 hrs Cat 1. Contact Janine Tash (916) 457-2267.

GENERAL/MULTIDISCIPLINARY

JANUARY 13-15, 2000: Health-Care Systems: Ethical and Economic Considerations. UC Davis Health System, UC Davis School of Medicine Alumni Association at Sacramento Hilton Inn, Sacramento, CA. 12 hrs Cat 1. Contact Vickie Hidalgo, (916) 734-5774; Fax (916) 734-8966, vickie.hidalgo@ucdmc.ucdavis.edu.

JANUARY 20-22, 2000: Women's Health 2000: Creating New Models for Comprehensive Care. Health Care Research Institute, Inc. and Postgraduate Institute for Medicine at The Radisson Hotel Sacramento, Sacramento, CA. 12 hrs Cat 1. Contact Lisa Tooker, 1 (800) 487-4325 or (916) 974-8688; lttoker@cme-webcredits.org

JANUARY 27-30, 2000: Medicine Meets Virtual Reality 2000–Envisioning Healing: Interactive Technology and the Patient-Practitioner Dialogue. Aligned Management Associates, Inc. and UC Irvine at Newport Beach Marriott Hotel, Newport Beach, CA. Contact (860) 447-9767; Fax (860) 444-0362; westwood@uconect.net; www.amainc.com.

COLORADO

To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850. Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences–Various Topics in Medicine. Lutheran Medical Center, Wheat Ridge. Contact Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month–Various Topics in Neurology. Colorado Society of Clinical Neurologists. Contact Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month–Cardiovascular Education Series. St Anthony Hospital at St Anthony Hospital, Denver. Contact Rose Powell, (303) 629-3678.

NOTICE

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Catherine Nancarrow, Editorial Manager,
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PO Box 7690, San Francisco, CA 94120-7690;
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JANUARY 17-21, 2000: Cardiovascular Conference at Snowmass. American College of Cardiology at Snowmass Conference Center, Snowmass, CO. 23 hrs Cat 1. Contact Registration Secretary, Extramural Programs Department, (800) 253-4636, ext 695; Fax (301) 897-9745.

JANUARY 30-FEBRUARY 3, 2000: Clinical Diabetes and Endocrinology in 2000. Bedford Conference Center, Aspen/Snowmass, CO. 21 hrs Cat 1. Contact Amy Muller, Medical Education Resources; (800) 421-3756 or (303) 798-9682; Fax (303) 798-5731; mer@dnvr.uswest.net; http://www.mer.org.

CONTACT INFORMATION
U of Colo–Contact University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; Fax (303) 372-9065.

IDAHO

To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930. Brochures, course information, and registration forms are available from the contact person or organization.

FEBRUARY 17-20, 2000: Ada County Medical Society 41st Annual Medical Winter Clinics. Sun Valley Inn, Sun Valley, ID. 12 hrs Cat 1. Contact Judy Barningham (208) 336-2930 or Marie Chester (208) 331-1478.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.
NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

Every First and Third Tuesday–Building and Implementing Clinical Practice Guidelines at the Point of Care. Contact Thomas A. Naegele, DO, (505) 275-7267.

JANUARY 13-16, 2000: Advanced Life Support in Obstetrics. UNM Continuing Education Conference Center, Albuquerque, NM. Contact UNM Continuing Medical Education, (505) 272-3942.

JANUARY 21-22, 2000: 30th Annual Winter Pediatric Orthopedic Seminar. UNM Continuing Education Conference Center, Albuquerque, NM. Contact UNM Continuing Medical Education, (505) 272-3942.

JANUARY 30-FEBRUARY 4, 2000: Options in Medical Education. Sheraton Old Town Hotel, Albuquerque, NM. Contact UNM Continuing Medical Education, (505) 272-3942.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Cat 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA98121; or phone (206) 441-9762 or (800) 552-0612.
Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

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Health care, technology, and human rights

David Heiden

At left, a Tibetan woman praying while lying on the operating table waiting for cataract surgery at the First People's Hospital, Lhasa, Tibet. September, 1995.

At right, the Dalai Lama's picture in a tea house in Lhasa, where display of his image has since been forbidden by the Chinese government. Tibetans believe that the Dalai Lama is the living re-incarnation of Chenrezig, the Bodhisattva of Compassion. September, 1995.

I went to Tibet in the fall of 1995 and 1997 to help with the problem of blindness. Blindness work is conceptually simple: most curable blindness is caused by cataract. Patient selection and surgical skills can be taught. The technology for curing cataract blindness has matured over the last 30 years, and now a superb operation can be done with simple tools at a cost of only $20 per eye, which includes implantation of a good quality artificial intraocular lens.

But after the skills and technology are introduced, then what happens? How many of the people with cataract blindness get surgery? It is not a big secret that for the last 40 years Tibetan religion and culture have been violently repressed. What should this mean to an expatriate trying to improve the health care system in Tibet? How should a doctor respond? Is there a link between human rights and good health care?

David Heiden is an ophthalmologist practicing in San Francisco.

3020

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